| Microscopic Observations | 0 | | 25 | | 50 | | 100 | | 250 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| **Stomach** - Pylorus Ulceration | | | | | 1 | | 1 | | 3 | 2 |
| **Small Intestine** - Ulceration/Erosion/Necrosis | | | | | 2 | 1 | 6 | 3 | 5 | 5 |
| Segmental Villus Blunting/Atrophy | | | | | 2 | | 3 | | | |
| Kidney - Papillary Necrosis/Pyelitis | | | | | | | 2 | 1 | | 1 |
| Interstitial Suppurative Nephritis/Fibrosis | | | | 1 | | | | | | |
| Brain - Chronic Perivascular/Periventricular Lymphocytic Infiltration | 1 | 1 | | | | 2 | 1 | 3 | 2 | 1 |
| Leptomeninges, Lymphocytic Infiltration, | | | 1 | | | | | | | 1 |
| Sternum Bone Marrow Hyperplasia | | | 1 | | | | 4 | 7 | 7 | 5 |
| Skin - Suppurative Subcutis Inflammation | | | | | 1 | | 1 | 1 | | 1 |

- PK Analysis - SC-58635 was absorbed and systemically available at all doses in both sexes during 4 week oral toxicity study. The $C_{max}$ and $AUC_{0-24\ hr}$ values for ♀ & ♂ following repetitive dosing were higher than $C_{max}$ and AUC values on Day 1 study, indicating that accumulation of SC-58635 occurred after repetitive dosing. Although highly variable values were seen among dogs, there was a trend that SC-58635 $C_{max}$ and AUC were higher in female dogs than those in male dogs. Mean PK parameters following are presented in the following table.

| Sampling Day | Dose mg/kg | $T_{max}$ (hr) | | $C_{max}$ ($\mu$g/ml) | | $AUC_{0-24}$ ($\mu$g•hr/ml) | |
|---|---|---|---|---|---|---|---|
| | | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| Day 1 | 25 | 1.8 | 2.0 | 1.72 | 1.90 | 18.65 | 21.68 |
| | 50 | 13.3 | 3.5 | 1.94 | 4.15 | 25.41 | 47.70 |
| | 100 | 3.2 | 6 | 3.96 | 6.89 | 71.02 | 103.64 |
| | 250 | 6.1 | 8.8 | 8.44 | 10.31 | 119.53 | 153.37 |
| Day 27 | 25 | 1.9 | 1.6 | 2.20 | 4.6 | 22.79 | 71.53 |
| | 50 | 1.8 | 1..9 | 4.66 | 6.77 | 60.56 | 83.73 |
| Day 15 | 100 | 10.2 | 5.7 | 8.72 | 8.35 | 103.72 | 117.25 |
| | 250 | 2.3 | 2.7 | 11.98 | 7.72 | 210.98 | 135.42 |



In conclusion, oral treatment of 25 mg/kg of SC-58635 to dogs appeared to be safe and results in no toxicological effects on survival, body weight and body weight gains and feed consumption. No treatment-related changes in any clinical and anatomical pathology parameters were seen. Dosages of 50, 100 and 250 mg/kg of SC-58635 were not tolerated. Ulceration of small intestine (mainly pylorus, jejunum duodenum and ileum) was the major test-related lesion in these animals. Dogs were more sensitive to SC-58635 induced GI toxicity as compared to rats. It was worthy to note that low incidence of interdigital pyoderma and subcutis abscess was identified in dogs at @ ≥50 mg/kg/day. Inconclusive histopathological changes in the brain (mild→moderate periventricular/perivascular lymphocytic infiltration) were noted.

2.2.1.7. 13-Week Capsule Toxicity Study With SC-58635 In Dogs, Document No: PSA95C-30-SA4324; Date: 01-Dec-1995 (Vol. 1.22-1.24)

Included as an appendix to this report were:

1. Evaluation Of The SC-58635 Plasma Concentration Data From The 13-Week Capsule Toxicity Study With SC-58635 In Dogs, Document No.: MRC95S-30-950261; Date: 20-Nov-1995
2. Metabolism Support For A 13-Week Capsule Toxicity Study With SC-58635 In Dogs, SA4324, Document No.: MRC95S-30-950263; Date: 27-Nov-1995
3. Final Report Amendment No. 1: Metabolism Support For A 13-Week Capsule Toxicity Study With SC-58635 In Dogs, SA4324, Document No.: M3196263; Date: 24-Sep-1997
4. Evaluation Of The Total Analyses And Liver Microsomal And Postmitochondrial Supernatant Preparation In A 13-Week Capsule Toxicity Study With SC-58635 In Dogs (SA4324), Document No.: MRC95C-30-950253; Date: 27-Nov-1995

Report Nº: 6127-233/PSA95C-30-SA4324, MRC95S-30-950263 (companion PK study), MRC95C-30-950253 (companion liver microsome study)

Study Nº: 6127-233/SA4324

Study Aim: To identify toxic effects of SC-58635 when administered orally to dogs for at least 13 weeks and reversibility of any toxic effects of the test compound following a 4-week recovery period.

Compound: SC-58635 (Lot Nº 94K014-A2B) and [$^{14}$C]SC-58635 (Lot Nº GDS 4404-164 & GDS 4404-165) in gelatin capsule

Vehicle: Empty gelatin capsule

Dosage: 0, 15, 25, and 35 mg/kg/day po for≥13 weeks

Animals: 30♂ & 30♀ beagle dogs, months old, weighing kg

| Main and Recovery[a] Study | | | | Satellite PK Study | | | |
|---|---|---|---|---|---|---|---|
| Group | Dose (mg/kg/dose) | Dose (mg/kg/day) | Nº of Animals/Sex | Group | Dose (mg/kg/dose) | Dose (mg/kg/day) | Nº of Animals |
| 1[a] | 0 | 0 | 6[c] | 6[a,b] | 7.5 | 15 | 3 |
| 2[a] | 7.5 | 15 | 4 | 7[a,b] | 12.5 | 25 | 3 |
| 3[a] | 12.5 | 25 | 4 | [a]Animals in Group 1-4, 6 and 7 were dosed twice daily at 12-hr intervals for ≥13 weeks. | | | |
| 4[a] | 17.5 | 35 | 6[c] | [b]Two animals/sex in group 1, 4, and 5 had a recovery phase for 28 days after a 13-week treatment. | | | |
| 5 | 25 | 25 | 4[c] | [c]Animals in group 6 and 7 received [$^{14}$C]SC-58635 at the first daily dose on Day 1 and once during weeks 6 and 13. | | | |

Study Location:

Study Date: March 10, 1995 - July 10, 1995

Compliance with GLP/QAU: Yes

Experimental Design: Dogs were given SC-58635, 0, 7.5x2, 12.5x2, 17.5x2 or 25x1 mg/kg/day in gelatin capsule orally gavage for at least 13 weeks; dosing continued through the day before terminal sacrifice (Day 93/94). Recovery animals were kept without treatment for an additional 4 weeks. Dogs in the companion PK study group received SC-58635 on Days 1, 39, 88 and received nonradiolabeled SC-58635 on other days during the study. The following observations were conducted:

- Clinical Signs and Mortality - 2x daily.
- Body Weights - Day 1, and weekly afterwards.
- Food Consumption - 1x/week.
- Physical examinations and ECGs (including heart rates) - 1x pre-℞ and once ~1-4 hr postdose during weeks 4, 8, and 13; and once during week 17 for the recovery animals.
- Ophthalmoscopic Examination - pre-℞ and during Weeks 8 and 12, and 17 (recovery animals).
- Clinical Laboratory Evaluation - pre-℞ and during Weeks 4, 8, 12, and week 17 (recovery animals). The parameters included in the clinical laboratory analysis are listed in the following table.

| HEMATOLOGY | | | |
|---|---|---|---|
| aPTT | WBC | MCH | Hb |
| PT | RBC | MCHC | Platelet Count |
| Differential WBC | Ht | MCV | Reticulocyte Count |

| URINALYSIS | | |
|---|---|---|
| Appearance/Color | Microscopic Examination Sediment | |
| Bilirubin | Protein | Volume |
| Glucose | pH | Specific Gravity |
| Ketones | Urobilinogen | |

| SERUM CHEMISTRY | | |
|---|---|---|
| ALT | | Potassium |
| Albumin | | Sodium |
| Alkaline Phosphatase | | Total Bile Acid |
| AST | | Total Bilirubin |
| Calcium | Chloride | Total Cholesterol |
| Creatinine | Glucose | Total Protein |
| Globulin | | Triglycerides |
| Inorganic Phosphorus | | Urea Nitrogen |

- PK/TK - Blood samples were collected at 0.5, 1, 2, 3, 4, 5, 7, 12, 13, 14, 15, 18 and 24 hr following the ingestion of radiolabeled ]SC-58635 on Days 1, 39, and 88. Urine and fecal samples were collected for 168 hr after each radiolabeled dose approximate 24-hr intervals.
- Necropsies - were performed on all animals at the end of the study (Week 13, 4/sex from Groups 1-4 and 2/sex from Group 5; Week 17, 2/sex from Groups 1, 4, and 5). At necropsy, the following organs (when present) were weighed. Paired organs were weighed together; the intestines were rinsed and blotted before weighing. Samples of liver (30-40 g) were collected for microsomal protein and cytochrome P450 content analyses.

| | | | |
|---|---|---|---|
| Adrenals | Intestine (small, cecum and colon) | Ovaries | Testes |
| Brain | Kidneys | Pituitary | Thymus |
| epididymis | Liver | Prostate | Thyroids with parathyroid |
| Heart | Lungs | Stomach | Uterus with cervix |

The following (when present) or representative samples were preserved in 10% phosphate-buffered formalin from animals in Groups 1-5 sacrificed after 13 weeks of treatment, unless otherwise specified:

| | | |
|---|---|---|
| Adrenals | Liver | Spinal Cord (Lumbar) |
| Aorta | Lungs | Spleen |
| Brain | Lymph Nodes (Mesenteric and Retropharyngeal) | Sternum with Bone Marrow |
| Cervix | Mammary Gland (♀ Only) | Stomach |
| Epididymides | Ovaries | Testes |
| Esophagus | Pancreas | Thymus |
| Eyes (Preserved in Davidson's Fixative) | Pituitary | Thyroids with Parathyroid |
| Femur with Bone Marrow (Articular Surface of the Distal End) | Prostate | Tongue |
| Gallbladder | Rectum | Trachea |
| Heart | Salivary Gland (Mandibular) | Urinary Bladder |
| Intestine, Small (Duodenum, Jejunum, Ileum) | Sciatic Nerve | Uterus |
| Intestine, Large (Cecum, Colon, Rectum) | Skeletal Muscle | Vagina |
| Kidneys | Skin | Lesions |

Tissues sections from above list of each dog in Groups 1, 4, and 5 were examined microscopically.

**Results:**

- Mortality & Clinical Observation - No deaths occurred. No remarkable clinical symptoms were treatment-related.
- Body Weight & Food consumption - No significant changes in mean body weights, cumulative body weight gains and food consumption.
- Ophthalmology - No significant findings were attributable to the treatment of SC-58635.
- ECG - Except 1♀ @ 25 mg/kg/day had a second degree AV block, all other dogs had normal ECG readings.
- Clinical Pathology - One ♂ @ 7.5 mg/kg bid had significantly elevated ALT activity (192 IU/l) during Week 4 analysis and had normal ALT values during the subsequent analyses (Weeks 8 and 12). A Group 5 ♂ (25 mg/kg qd) had significantly increased WBC ($31x10^3/\mu l$) and absolute PMN counts ($27.5x10^3/\mu l$) during Week 8, an indicative of ongoing inflammation. An abscess was found in the area of lower right mandible of this dog. Leukogram of this dog at Week 12 was normal.
- Pathology & Histology - No treatment related alterations were noted macro- or microscopically.
- Toxicokinetics -

  Absorption: Oral administration of SC-58635 was absorbed and systemically available. Plasma concentrations of SC-58635 and the exposure to SC-58635, as measured by AUC, increased with dose. The mean plasma concentration and AUC on Day 88 are shown in the following table.

| Group | Dose (mg/kg) | Dosage (mg/kg/day) | $C_{max}$ (μg/ml) | | $AUC_{0-24}$ (μg•hr/ml) | |
|---|---|---|---|---|---|---|
| | | | ♂ | ♀ | ♂ | ♀ |
| 2 | 7.5 | 15 | 1.32 ± 0.376 | 1.67 ± 0.570 | 13.8 ± 4.54 | 14.2 ± 5.27 |
| 3 | 12.5 | 25 | 1.83 ± 0.358 | 1.64 ± 0.337 | 18.0 ± 4.23 | 15.8 ± 6.14 |
| 4 | 17.5 | 35 | 2.59 ± 0.525 | 2.68 ± 0.427 | 25.7 ± 5.66 | 29.4 ± 6.75 |
| 5 | 25 | 25 | 0.875 ± 0.310 | 0.473 ± 0.040 | 10.1 ± 5.28 | 3.98 ± 1.52 |

Summary of $C_{max}$, $T_{max}$, and AUC of plasma and erythrocyte radioactivity concentrations following a single oral dose of ]SC-58635 to male and female dogs on Day 1, and during Weeks 6 and 13 of a 13-Week dosing regimen are shown in the following table.

| Sample | Dose mg/kg/day | Duration | $C_{max}$ (μg eq./g) | $T_{max}$ (hr) | $AUC_{0-t}$ (μg eq.•hr/g) |
|---|---|---|---|---|---|
| Plasma | 7.5 | Day 1 | | | |
| | | Week 6 | | | |
| | | Week 13 | | | |
| | 12.50 | Day 1 | | | |
| | | Week 6 | | | |
| | | Week 13 | | | |
| RBC | 7.50 | Day 1 | | | |
| | | Week 6 | | | |
| | | Week 13 | | | |
| | 12.50 | Day 1 | | | |
| | | Week 6 | | | |
| | | Week 13 | | | |

A summary of $C_{max}$, $T_{max}$, and AUC of plasma and erythrocyte radioactivity concentrations following a single oral dose of ]SC-58635 on Day 1, and during Weeks 6 and 13 of a 13-Week dosing regimen in dogs classified as fast or slow metabolizers of SC-58635 is given in the table below.

| Sample | Dose mg/kg/day | Duration | $C_{max}$ (μg eq./g) | | $T_{max}$ (hr) | | $AUC_{0-t}$ (μg eq.•hr/g) | |
|---|---|---|---|---|---|---|---|---|
| | | | Fast | Slow | Fast | Slow | Fast | Slow |
| Plasma | 7.5 | Day 1 | | | | | | |
| | | Week 6 | | | | | | |
| | | Week 13 | | | | | | |
| | 12.50 | Day 1 | | | | | | |
| | | Week 6 | | | | | | |
| | | Week 13 | | | | | | |
| RBC | 7.50 | Day 1 | | | | | | |
| | | Week 6 | | | | | | |
| | | Week 13 | | | | | | |
| | 12.50 | Day 1 | | | | | | |
| | | Week 6 | | | | | | |
| | | Week 13 | | | | | | |

Excretion: The major excretion route was through feces. A summary of the percent of radioactive dose excreted in urine and feces of dogs (Groups 6 and 7) following a single oral dose of ]SC-58635 on Day 1, and During Weeks 6 and 13 of a 13-Week dosing regimen is listed in the following table.

| Group | Dose mg/kg/day | Dosing Interval | % Radioactive Dose | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Urine | | Feces | | Total | |
| | | | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| 6 | 7.50 | Day 1 | 0.49 | 0.56 | 96.2 | 105 | 96.9 | 106 |
| | | Week 6 | 0.77 | 0.73 | 91.8 | 92.2 | 92.8 | 93.2 |
| | | Week 13 | 0.41 | 0.87 | 94.1 | 90.9 | 94.8 | 92.4 |
| 7 | 12.50 | Day 1 | 0.64 | 1.25 | 93.9 | 92.5 | 95.1 | 94 |
| | | Week 6 | 0.43 | 1.06 | 90.8 | 96.4 | 91.3 | 97.9 |
| | | Week 13 | 0.37 | 1.35 | 92.2 | 90.3 | 93.3 | 92.3 |

Metabolic Profile in Urine and Feces: Majority of drugs excreted in the feces were as unchanged , parent drug and SC-62807 ( ., the carboxylated metabolite. Mean (±SEM) percent of dose excreted in feces (0-72 hr) as SC-58635 and SC-62807 on Weeks 1, 6 and 13 in dogs characterized as having a fast or a slow SC-58635 clearance are presented as follows:

| Group | Week | % of dose excreted as SC-58635 | | % of dose excreted as SC-62807 | |
|---|---|---|---|---|---|
| | | Fast | Slow | Fast | Slow |
| 6 | 1 | 78 ± 11.5 | 84.7 ± 1.63 | 26.7 ± 10.8 | 9.78 ± 4.4 |
| 7 | | 82.9 ± 1.0 | 57.1 ± 9.7 | 10.3 ± 1.5 | 29.2 ± 13 |
| 6 | 6 | 68.9 ± 13.2 | 66.4 ± 11.2 | 20.9 ± 10.8 | 25.4 ± 10.9 |
| 7 | | 75.5 ± 2.6 | 68.8 ± 9.7 | 13.7 ± 3.4 | 26.5 ± 16.8 |
| 6 | 13 | 70.7 ± 7.7 | 78 ± 11.7 | 20.6 ± 8.2 | 14.9 ± 9.7 |
| 7 | 3 | 68.9 ± 12 | 72 ± 13 | 21.4 ± 10.5 | 19.1 ± 12 |

The following table shows mean (±SEM) percent of dose excreted in feces (0-72 hours) as SC-58635 and SC-62807 on Weeks 1, 6 and 13 of dose administration in male and female dogs.

| Group | Week | % of dose excreted as SC-58635 | | % of dose excreted as SC-62807 | |
|---|---|---|---|---|---|
| | | ♂ | ♀ | ♂ | ♀ |
| 6 | 1 | 75.6 ± 9.9 | 87.1 ± 3.8 | 19.4 ± 9.5 | 17.1 ± 10.8 |
| 7 | | 77.4 ± 4.6 | 62.6 ± 13.6 | 11.5 ± 0.7 | 27.9 ± 13.9 |
| 6 | 6 | 65.6 ± 12 | 69.7 ± 12.5 | 24 ± 9.6 | 22.3 ± 12.2 |
| 7 | | 75.8 ± 2.7 | 68.4 ± 9.5 | 14.6 ± 2.8 | 25.6 ± 17.2 |
| 6 | 13 | 78.2 ± 11.5 | 70.5 ± 7.8 | 15.6 ± 10.4 | 19.9 ± 7.6 |
| 7 | | 77.3 ± 12.7 | 63.7 ±10.4 | 14.3 ± 11.1 | 26.1 ± 9.9 |

Metabolism: It apperaed that higher portions of SC-58635 transformed into SC-60613, a hydroxyl metabolite, in the microsomes obtained from fast metabolizers. The following table lists mean (±SEM) percent of SC-58635 and SC-60613 in dog liver microsomes incubated with SC-58635 from ♂ and ♀ dogs characterized as having a fast or slow SC-58635 clearance.

| Dose | % SC-60613 | | | | % SC-58635 | | | |
|---|---|---|---|---|---|---|---|---|
| (mg/kg/day) | Male | Female | Fast | Slow | Male | Female | Fast | Slow |
| Control | 14.60 ± 4.40 | 14.00 ± 1.40 | 16.10 ± 2.50 | 9.00 | 71.30 ± 6.00 | 78.10 ± 1.70 | 73.70 ± 4.00 | 77.70 |
| 15.00 | 15.50 ± 5.30 | 14.80 ± 4.60 | 22.40 ± 3.70 | 7.88 ± 0.62 | 77.90 ± 5.70 | 84.50 ± 4.70 | 73.70 ± 4.30 | 88.70 ± 2.10 |
| 35.00 | 19.70 ± 6.70 | 10.80 ± 1.20 | 22.10 ± 5.30 | 8.45 ± 0.28 | 79.60 ± 6.70 | 88.90 ± 1.20 | 77.40 ± 5.40 | 91.20 ± 0.30 |

Microsome Induction: Similar levels of total cytochrome P450 content, microsomes and total protein yield of dog liver were obtained as shown in the following table.

| Group | Dose | P450 (nmole/mg protein) | | Microsome Yield (mg/g liver) | | Total Protein Yield | |
|---|---|---|---|---|---|---|---|
| | mg/kg/day | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| 1[a] | Control | | | | | | |
| 2 | 15 | | | | | | |
| 3 | 25 | | | | | | |
| 4 | 35 | | | | | | |
| 5 | 25 | | | | | | |

[a] Total daily dose administered. Animals in Groups 1 through 4 were dosed twice daily for at least 13 weeks. Animals in Group 5 were dosed once daily for at least 13 weeks.

[b] Mean ± SD.

No treatment-associated changes were observed in all dose groups. Therefore, the MTD was not achieved in present study.

2.2.1.8. Seven-Day Exploratory Intravenous Toxicity Study Of SC-58635 In The Dog (EX4381), Document No.: P30E4381; Date: 26-Nov-1997

Included as an appendix to this report was:

Evaluation Of Plasma Concentration Data From The Seven Day Exploratory Intravenous Toxicity Study Of SC-58635 In The Dog, EX4381, Document No.: M3095222; Date: 12-Aug-1996

Study Nº: EX4381
Report Nº: P30E4381
Study Aims: To assess the relationship of plasma levels of SC-58635 to gastrointestinal injury in the dog and to establish a correlation between plasma levels of SC-58635 and biochemical changes (i.e., prostaglandin levels) in potential target organs.
Compound: SC-58635 (Lot Nº 94KO14-A3B in Phase 1; Lot Nº GDS-4695-042 in Phase 2).
Vehicle Control: PEG/sterile $H_2O$ (2:1 on Day 1 of Phase 1 or 3:1 on Days 2-7 of Phase 1 and all of Phase 2)
Dose & Route: 0, 15 or 40 mg/kg/ml iv for 7 days
Animals: ♂ & ♀ Beagle dogs, months of age, weighing kg for Phase 1 study; months old and weighing kg for Phase 2 study.
Study Location: Searle R&D, Skokie, IL (in-life & pathology) and CEDRA Corporation, Austin, TX (analysis of plasma concentrations of SC-58635).
Study Date: Phase 1 - treatment: 7/6-7/12/95; Sacrificed: 7/13/95.
Phase 2 - Treatment: 11/30-12/6/95; Sacrificed: 12/7/95.
GLP/QAU Compliance: N/A
Study Design: Groups of 3 dogs, randomly assigned to dose groups as shown in the following table, were administered intravenously (iv) with SC-58635 at 0, 15 or 40 mg/kg daily for 7 days.

| Group | Dose (mg/kg) | Nº of Animals |
|---|---|---|
| PHASE 1 STUDY | | |
| 1 | 0 | 3 |
| 2 | 15 | 3 |
| PHASE 2 STUDY | | |
| 1 | 0 | 3 |
| 2 | 40 | 3 |



The following observations were conducted. The concentrations of SC-58635 in plasma were determined using

- Physical Examinations - Day 1 pre-℞.
- Mortality & Clinical Signs - 2x/day; pre-℞ and ~1-3 hr after dosing.
- Body Weights - 2x pre-℞ and 2x during the treatment.
- PK - Blood samples for pharmacokinetic assessments were collected from each dog in Phases 1 and 2 at 5, 15, and 30 min and 1, 2, 4, 6, 8 and 24 hr after dosing on Days 1 and 7.
- Ex Vivo Analysis for Inhibition of COX-1 and COX-2 Activities in Blood - Days 1, 4, and 7; pre-℞ and 24 hr after dosing.
- Clinical Pathology - Day 8 before necropsy. The following parameters were analyzed.

| HEMATOLOGY PARAMETERS | | COAGULATION PARAMETERS | CHEMISTRY PARAMETERS |
|---|---|---|---|
| White Blood Cells | MCV | Activated Partial Thromboplastin Time | Alanine Aminotransferase |
| Differential WBC | MCH | Prothrombin Time | Total Protein |
| Red Blood Cells | MCHC | Fibrinogen | Albumin |
| Hb Ht | Platelets | | Calcium |

Necropsy - Day 8. Macroscopic observations were recorded. Specified organs and selected tissues as shown in the following table were collected and preserved for microscopic evaluation. Tissues designated with an asterisk were weighed and paired organs were weighed together.

| | | |
|---|---|---|
| *Large Intestine (Colon and Cecum-Opened, Washed and Weighed Separately) | *Kidneys (Both) | Lesions |
| *Intestine, Small (Duodenum, Jejunum, Ileum-Opened, Washed and Weighed Together) | *Stomach | |

- Prostaglandin Analysis - Approximately 5 grams of stomach, jejunum, colon, and kidney were frozen in liquid nitrogen for analysis of prostaglandin content.

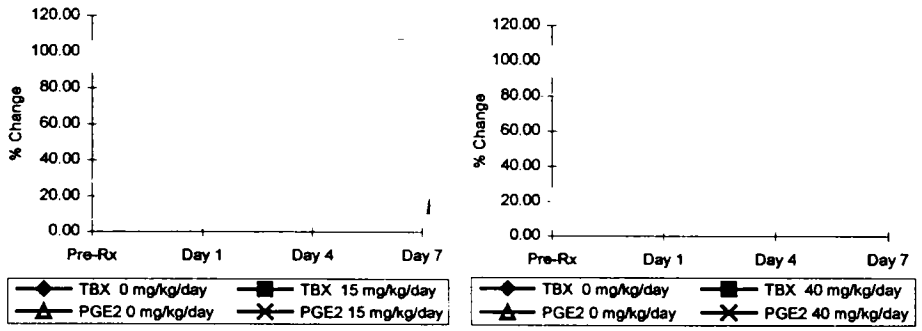
**Results:**

- Clinical Signs and Mortality - No deaths occurred. Swelling of the forelimbs was seen in dogs receiving test article. This forelimb swelling was more extensive in Phase 2 animals. Moreover, in one animal, the swelling extended from the forelimbs to involve the chest, ventral thorax, and neck.
- Body Weights - No significant changes were noted.
- Clinical Pathology - Elevated ALT values were noted in one dog each @ 0 (~2x ↑) and 15 mg/kg (4x ↑) on Day 8 of Phase I study. Increases in relative (82 vs 57%) and absolute neutrophil (16.57 vs 6.33 $x10^3/\mu l$) and total WBC (11.1 vs 20.5 $x10^3/\mu l$) counts, and ↓ in mean total protein (↓11%) and albumin (↓16%) values were noted in the dogs at 40 mg/kg on Day 8 during Phase II study.
- Tissue $PGE_2$ Levels (pg/g tissue)-

| Tissue | PHASE 1 | | PHASE 2 | |
|---|---|---|---|---|
| | 0 mg/kg/day | 15 mg/kg/day | 0 mg/kg/day | 40 mg/kg/day |
| Stomach | 3406.2 ± 1677 | 1163.1 ± 194 | 1950 ± 283 | 1195 ± 509 |
| Kidney | 111.2 ± 48.3 | 42.7 ± 16.9 | 148.4 ± 52.3 | 28.0 ± 10.7 |
| Jejunum | 462.6 ± 22.2 | 413.9 ± 115 | 959.7 ± 122 | 604.8 ± 171 |
| Colon | 1022.9 ± 54.8 | 977.9 ± 232 | 1068.1 ± 463 | 893.3 ± 90.7 |

- Ex Vivo Analysis for Inhibition of COX-1 (TBX Levels) and COX-2 ($PGE_2$ Levels) Activities in Blood - The levels and percent changes of TBX and $PGE_2$ in the blood on different days during Phase I and II studies are shown in the following table and figures.

| Sampling Day | Blood TBX Levels (ng/ml) | | | | Blood $PGE_2$ Levels (ng/ml) | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 mg/kg/day | 15 mg/kg/day | 0 mg/kg/day | 40 mg/kg/day | 0 mg/kg/day | 15 mg/kg/day | 0 mg/kg/day | 40 mg/kg/day |
| Pre-Rx | 41.4 | 150.5 | 43.4 | 19.5 | 3225 | 2626 | 900 | 442 |
| Day 1 | 36.0 | 39.3 | 28.0 | 11.2 | 1782 | 235 | 954 | 57 |
| Day 4 | 25.3 | 23.3 | 38.7 | 9.5 | 2440 | 190 | 758 | 187 |
| Day 7 | 28.7 | 22.5 | 29.4 | 5.7 | 3696 | 497 | 1031 | 208 |




- Mean PK (±SEM) parameters for SC-58635 on Days 1 and 7 following iv administration of SC-58635 to the dog are summarized in the following table.

| Dose (mg/kg) | Day | $T_{max}$ (hr) | $C_{max}$ ($\mu$g/ml) | $AUC_{0-\infty}$ ($\mu$g•hr/ml) |
|---|---|---|---|---|
| 15.0 | 1 | 2.17 ± 1.92 | 3.38 ± 0.09 | 59.1 ± 8.4 |
| 15.0 | 7 | 3.50 ± 1.61 | 5.35 ± 1.08 | 74.7 ± 11.8 |
| 40.0 | 1 | 0.08 ± 0 | 32.8 ± 2.3 | 137 ± 5 |
| 40.0 | 7 | 0.08 ± 0 | 32.5 ± 3.8 | 143 ±11 |

- Gross and Histopathology - There were no remarkable changes in organ weights. Moderate edema of the subcutis and musculature of the right forelimb, a response to perivascular leakage

of test article/vehicle, was observed in one Phase 1 and all Phase 2 SC-58635 treated dogs. Two shallow ulcers (approximately 1 cm in diameter) were identified in the proximal duodenum (pyloric-duodenal junction) of one animal given 40 mg/kg SC-58635. Other gross findings in this animal included the abundant dark black contents (melena) in the ileum and colon, swollen kidneys, pallor of the renal papilla, edema around the kidneys (perirenal) and omentum, and enlarged mesenteric lymph nodes. Treatment-related histomorphologic changes correlated with the lesions noted macroscopically, were moderate focal subacute ulceration in the proximal small intestine at the pyloric duodenal junction of one Phase 2 dog receiving 40 mg/kg SC-58635. Microscopic evaluation of the forelimb injection sites of 2 Phase 2 animals revealed moderate to marked subacute necrotizing vasculitis with thrombosis involving primarily large veins, moderate to marked diffuse edema with multifocal hemorrhages, and multifocal infiltrates of a mixed population of inflammatory cells (predominantly neutrophils and macrophages).

Based on presented results, it appeared to be high levels of $PGE_2$ present in the stomach and colon. Treatment with SC-58635 caused decreases in blood TBX and $PGE_2$ levels. At a dose of 40 mg/kg, SC-58635 caused GI lesions (pyloric-duodenal ulcer/erosion) in the dog after repeated dosing for 7 days.

### *2.2.2. CHRONIC TOXICITY STUDIES*

#### 2.2.2.1. 26-Week Repeated Dose Oral Gavage Toxicity Study In Rats With SC-58635 (SA 4366), Document No: P30S4366; Date: 16-Sep-1996 (Vol. 1.26-1.28)

Included as an appendix to this report was:

1. Pharmacokinetics And Metabolism Support For A 26-Week Oral Toxicity Study Of SC-58635 In Rat, Document No.: M3096054; Date: 04-Jun-1996
2. Final Report Amendment No. 1: Pharmacokinetics And Metabolism Support For A 26-Week Oral Toxicity Study Of SC-58635 In The Rat, SA4366, Document No.: M3196054; Date: 07-Oct-1997
3. Final Report Amendment No. 1: 26-Week Repeated Dose Oral Gavage Toxicity Study In Rats With SC-58635 (SA4366), Document No.: P31S4366; Date: 07-Oct-1997

| | |
|---|---|
| Report Nº: | M3096054 |
| Study Nº: | SA4366/ 700-331 |
| Study Aim: | To evaluate the chronic toxicity of SC-58635 in rats following a daily oral gavage administration for ≥26 weeks. |
| Compound: | SC-58635 (Lot Nº 94K014-A2B), SC-58635 (Lot Nº GDS4021-68 & Lot Nº 4404-145 |
| Control Vehicle: | 0.5% (w/v) methylcellulose and 0.1% Polysorbate 80 in distilled $H_2O$ |
| Dose & Route: | 0, 20, 80, 400 mg/kg/day po by gavage |
| Animals: | Sprague-Dawley rats, Crl:CD®(SD)BR, ~6 weeks of age, weighing g for ♂ and g for ♀, 25/sex/group for main (15/sex/group) and recovery (10/sex/group) studies, 18/sex/group for satellite PK study. |
| Study Location: | |
| GLP/QAU Compliance: | Yes |
| Study Date: | 03/06/95 - 10/12/95 |

Study Design: Animals were given SC-58635, 0, 20, 80, or 400 mg/kg/day by oral gavage once daily for at least 26 weeks. Ten rats/sex from groups 1-4 were allowed to have a 4-week recovery period after the last dosing. Animal group designation and dosing levels are shown in the following table. On Days 1 and 177, SC-58635 was given to Groups 5, 6, and 7 animals. Blood samples

were collected at 0.5, 1.0, 2.0, 3.0, 4.0, 8.0, and 24 hr post dosing from 3 rats/sex/time point. Urine and fecal samples were collected over 168 hr after dosing with SC-58635 in 24 hr intervals.

| Main and Recovery[a] Study | | | | Satellite PK Study | | | |
|---|---|---|---|---|---|---|---|
| Group | Dose (mg/kg/day) | Nº of Animals | | Group | Dose (mg/kg/day) | Nº of Animals | |
| | | ♂ | ♀ | | | ♂ | ♀ |
| 1 | 0 (MC) | 25 | 25 | 5 | 20 (Low) | 18 | 18 |
| 2 | 20 (Low) | 25 | 25 | 6 | 80 (Mid) | 18 | 18 |
| 3 | 80 (Mid) | 25 | 25 | 7 | 400 (High) | 18 | 18 |
| 4 | 400 (High) | 25 | 25 | [a]The recovery group comprised of 10/sex/group | | | |

The following observations were conducted:

- Mortality and Clinical Signs - 2x/day during treatment and 1x/day during recovery phase.
- Body Weights - Day 1 pre-R, 2x/week up to Week 4, and 1x/week thereafter.
- Food Consumption - 1x/week.
- Ophthalmoscopic Examinations - Pre-R and Week 26.
- Clinical Pathology (Groups 1-4) - Weeks 13 (10/sex/group), 27 (terminal sacrifices) and, 31 (recovery sacrifices). Urine specimens were obtained from animals in individual urine collection cages. The specimens for routine urinalysis were obtained following 4 hours (±15 min) of collection. Collections continued for a total of 22 hours (±15 min) and the total volume was recorded after the final collection. The following parameters were determined:

| HEMATOLOGY | | SERUM CHEMISTRY | |
|---|---|---|---|
| aPTT | MCH | ALT | Inorganic Phosphorus |
| PT | MCHC | Albumin | Potassium |
| Differential Count and Cell Morphology | MCV | Albumin/Globulin Ratio | Protein Electrophoresis |
| WBC | Mean Platelet Volume | Alkaline Phosphatase | Sodium |
| RBC | Platelet Count | AST | Sorbitol Dehydrogenase |
| Ht | Reticulocyte Count | Calcium | Total Bilirubin |
| Hb | | Chloride | Total Cholesterol |
| ROUTINE URINALYSIS | | Creatinine | Total Protein |
| Appearance/Color | Occult Blood | Globulin | Triglycerides |
| Bilirubin | pH | Glucose | Urea Nitrogen |
| Glucose | Protein | URINE CHEMISTRY | |
| Ketones | Urobilinogen | Urine Sodium | Urine Osmolality |
| Microscopic Sediment | | Urine Potassium | Total Volume |

- PK/TK - Blood was collected from Groups 5-7 (3/sex/time point) on Days 1 and 177 at 0.5, 1, 2, 3, 4, 6, 8, and 24 hr post radiolabeled dose. Fecal and urine samples were collected from the designated animals (3/sex/group) in Groups 5-7 for 7 days after SC-58635 administration.
- Necropsy - Necropsy was performed on all unscheduled deaths and surviving animals in Groups 1-4. The following organs (from post-treatment and recovery sacrifice animals) were weighed at necropsy.

| | | | | |
|---|---|---|---|---|
| Adrenals | Kidneys | Ovaries | Stomach (Empty) | Uterus |
| Brain (with Brainstem) | Heart | Pituitary (Postfixation) | Testes with Epididymides | |
| Cecum (Empty) | Liver | Prostate | Thymus | |
| Colon (Empty) | Lung | Spleen | Thyroid with Parathyroids (Postfixation) | |

The following tissues (when present) from each main and recovery study animal were preserved in 10% neutral-buffered formalin. Tissues from the main and recovery study animals in Groups 1 and 4 and animals in Groups 1-4 that were found dead or sacrificed in extremis were examined microscopically. In addition, the liver, kidneys, small intestines, and large intestines animals in Groups 2 and 3 were examined. Gross lesions were examined from all animals.

| | | |
|---|---|---|
| Adrenals (Both) | Lung (with Bronchi) | Spleen |
| Aorta (Thoracic) | Mammary Gland with Skin | Stomach |
| Bone Marrow (Femur and Sternum) | Mesenteric Lymph Node | Testes with Epididymides (Both) |
| Brain with Brainstem (Medulla/Pens, Cerebella Cortex, and Cerebral Cortex) | | Thigh Musculature |
| Large Intestine (Colon, Cecum, Rectum) | Ovaries (Both) | Thymus |
| Small Intestine (Duodenum, Jejunum, Ileum) | Pancreas | Thyroid (Parathyroids) |
| Eyes (Both with Optic Nerve) | Pituitary | Tongue |
| Femur Including Articular Surface | Prostate | Trachea |
| Harderian Gland | Salivary Glands (Mandibular) | Urinary Bladder |
| Heart | Sciatic Nerve | Uterus with Vagina and Cervix |
| Kidneys (Both) | Seminal Vesicle | Lesions |
| Liver | Spinal Cord (Cervical, Mid-Esophagus Thoracic, and Lumbar) | |

**Results:**

- Mortality and Clinical Signs - There were a total of 7 treatment-related deaths (1♀ @ 80 mg/kg, Week 25; 6♀ @ 400 mg/kg, Weeks 15-22) as a result of GI injury (GI necrosis with moderate→severe peritonitis). One ♀ at 80 mg/kg died of pulmonary hemorrhage due to gavage accident during Week 15. No remarkable clinical symptoms were attributable to the treatment. The survivals for each group at Week 26 are listed in the following table.

| | Dose (mg/kg/day) | | | |
|---|---|---|---|---|
| | Control | 20 | 80 | 400 |
| ♂ | 25/25 | 25/25 | 25/25 | 25/25 |
| ♀ | 25/25 | 25/25 | 23/25 | 19/25 |



- Body Weights and Food Consumption - Comparable mean body weight values were noted for rats in all groups. Significantly higher values in mean body weight changes were noted in Group 3 ♂ during Weeks 1 (↑ 26%), 11 (↑ 27%), and 22 (↑ 600%) and Group 4 ♀ during Week 3 (Days 19-22) (↑ 71%). Significantly lower mean body weight gains were noted in Group 4 ♂ during Weeks 14 (↓ 50%) and 17 (↓ 70%) and Group 3 ♀ during Week 11 (↓ 60%). However, there were no significant differences in total body weight change values during treatment (Weeks 1-26). As for food consumption, sporadically significant changes were noted (↑6% and 11%, respectively in Group 4 ♀ during Weeks 4 and 18; ↓7% in Group 4 ♂ during week 25).
- Ophthalmology - No treatment related changes were observed.
- Clinical Pathology - There were no significant changes in hematology and serum chemistry analyses. No remarkable findings were noted in urinalysis. Elevated osmolality with higher values in urine $K^+$ were noted in SC-58635 treated 4 ♂ during Week 13 analysis. These changes might not have biological impacts as they were not observed in the subsequent analyses (Weeks 27 terminal sacrifices and 31 recovery sacrifices).
- PK/TK -

  Absorption: SC-58635 was absorbed systemically following oral administration. Mean PK parameters for SC-65872 on Day 182 are presented in the following table. Dose-dependent but not proportional increases in AUC and $C_{max}$ values were noted. Higher exposure of SC-58635, as measured by AUC and $C_{max}$, was seen in female rats.

| Parameters | Dose Levels (mg/kg) | | | | | |
|---|---|---|---|---|---|---|
| | 20 | | 80 | | 400 | |
| | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| $C_{max}$ (μg/ml) | 2.03 | 4.05 | 2.97 | 6.94 | 5.12 | 10.5 |
| $AUC_{0-24}$ (μg•hr/ml) | 26.5 | 52.5 | 41.5 | 101 | 54.6 | 150 |
| $T_{max}$ (hr) | 2 | 4 | 2 | 6 | 1 | 3 |

  Relationship between Plasma Concentrations and Dose: Majority , of the radioactivity circulating in plasma on Day 177 was SC-58635. Small percentages of radioactivity circulating in plasma from rats in the 20 and 80 mg/kg dose groups were the hydroxylated

metabolite, SC-60613 , and the carboxylated metabolite, SC-62807 Only unchanged drug, SC-58635, was detected in the plasma from animals @ 400 mg/kg.
Excretion and Metabolic Profiles in Urine and Feces: The majority of radioactivity excreted in urine (0-48 hr) was SC-62807 representing of the dose. Less than 1% of the dose was excreted as unchanged drug in the urine. The majority of the fecal radioactivity excreted in feces (0-72 hr) was SC-58635 and SC-62807 representing and of the dose, respectively. A higher percentage of the dose was excreted as SC-58635 and a lower percentage of the dose was excreted as SC-62807 with increasing dose level.

- Histopathology - The major treatment-related pathological changes were limited to GI tract. These alterations were characterized as severe necrosis in jejunum (Group 3: 1♂ & 1♀; Group 4: 4♀) and various degree of chronic active inflammation of the abdominal serosal surface.

Therefore, treatment of SC-58635 to rats for 26 weeks by oral gavage caused deaths and GI injury at doses ≥80 mg/kg/day.

2.2.2.2. 52-Week Capsule Toxicity Study With SC-58635 In Dog, (SA 4425) (26-Week Interim Evaluation), Document No: P3IS4425; Date: 23-Sep-1996 (Vol. 1.29-1.30)

Included as an appendix to this report was:
Evaluation Of The SC-58635 Plasma Concentration Data From The 52-Week Capsule Toxicity Study With SC-58635 In Dogs, SA4425, Document No.: M3096285; Date: 18-Sep-1996

Study Nº: SA4425/6127-190/700-338
Report Nº: P3IS4425
Study Aim: (1) To identify toxic effects of SC-58635 when administered orally to dogs for at least 52 weeks and reversibility of any toxic effects of the test compound following a 4-week recovery period; (2) To determine the relationship of plasma concentration of test material to the duration of dosing; and (3) To evaluate evidence for sex-related differences in PK parameters.
Compound: SC-58635 (Lot Nº 94K014-A2B)
Vehicle: Empty gelatin capsule
Dosage: 0, 15, 25, and 35 mg/kg/day po for 52 weeks
Animals: 56 & 56 beagle dogs, ~7 months old, weighing kg for ♂ and g for ♀.

| Main and Recovery Study | | | | Satellite PK Study | | | |
|---|---|---|---|---|---|---|---|
| Group | Dose (mg/kg/dose) | Dose (mg/kg/day) | Nº of Animals/Sex | Group | Dose (mg/kg/dose) | Dose (mg/kg/day) | Nº of Animals/Sex |
| 1 | 0 | 0 | 12 | 6 | 7.5 | 15 | 4 |
| 2 | 7.5 | 15 | 8 | 7 | 12.5 | 25 | 4 |
| 3 | 12.5 | 25 | 8 | 4/sex from Groups 1-5 were sacrificed at Week 26. | | | |
| 4 | 17.5 | 35 | 12 | Dogs in Groups 1-4 & 6-7 received SC-58635 2x/day. | | | |
| 5 | 25.0 | 25 | 8 | Dogs in Groups 6 & 7 received SC-58635 as 1st daily dose on Day1 and Weeks 26 and 52. | | | |

Study Location:

Compliance with GLP/QAU: Yes
Experimental Design: Dogs were given SC-58635, 0, 7.5x2, 12.5x2, 17.5x2 or 25x1 mg/kg/day in gelatin capsule orally gavage for at least 52 weeks; dosing continued through the day before terminal sacrifice (Week 52). Recovery animals were kept without treatment for an additional 4

weeks. Dogs in the companion PK study group received [ ]SC-58635 on Days 1, 176 & 358 and received nonradiolabeled SC-58635 on other days during the study.
The following observations were conducted.

- Clinical Signs, Mortality, and Moribundity - 2x/day.
- Body weights - Day 1 Pre-R, and 1x/week afterwards.
- Food consumption - 1x/week.
- Physical examinations (including rectal temperatures and respiration rates) and ECGs (Leads I, II, and III, aVR, aVL, aVF, $rV_2$, $V_2$, $V_4$, and $V_{10}$) (including heart rates) - 1x Pre-R and 1x 1-4 hr postdose during weeks 13, 26, 39 and 52.
- Ophthalmoscopic - pre-R and Weeks 26 and 52.
- Clinical Laboratory Evaluations - 1x pre-R and Weeks 13, 26, 39, 52 and 56. The parameters included in the clinical laboratory analysis are listed in the following table.
  The parameters included in the clinical laboratory analysis are listed in the following table.

| HEMATOLOGY | | | | SERUM CHEMISTRY | | |
|---|---|---|---|---|---|---|
| aPTT | WBC | MCH | Hb | ALT | Globulin | Glucose |
| PT | RBC | MCHC | Platelet Count | Albumin | Inorganic Phosphorus | |
| Differential WBC | Ht | MCV | Reticulocyte Count | Albumin/Globulin Ratio | Potassium | Sodium |
| URINALYSIS | | | | Alkaline Phosphatase | Total Bile Acid | |
| Appearance/Color | Occult Blood | | Ketones | AST | Total Bilirubin | |
| Bilirubin | pH | | Urine Potassium | Calcium | Total Cholesterol | |
| Glucose | Protein | | Urine Sodium | γ-Glutamyltransferase (γ-GT) | Total Protein | |
| Microscopic Examination Sediment | | | Total Volume | Chloride | Triglycerides | |

- PK/TK - Blood samples were collected at 0.5, 1, 2, 3, 4, 5, 7, 12, 13, 14, 15, 18 and 24 hr following the ingestion of radiolabeled [ ]SC-58635. Urine and fecal samples were collected for 168 hr after each radiolabeled dose approximate 24-hr intervals.
- Necropsies - Week 26 (interim sacrifice: Groups 1-5, 4/sex/group). The following organs were weighed. Organ-to-terminal-body-weight and organ-to-brain-weight ratios were calculated.

| | | |
|---|---|---|
| Adrenals | Large Intestine (Cecum and Colon) | Small Intestine (Duodenum, Jejunum, Ileum) |
| Brain (with Brainstem) | Ovary | Stomach |
| Heart | Pituitary | Testes With Epididymides |
| Kidneys | Prostate | Thyroids (with Parathyroid) |
| Liver with Drained Gallbladder | | Uterus with Cervix |

The following tissues (when present) from each animal were preserved in 10% neutral-buffered formalin. Microscopic evaluations were performed on all tissues from animals in Groups 1 and 4 sacrificed at Week 26.

| | | | | |
|---|---|---|---|---|
| Adrenals | Mammary Gland (♀ Only) | | Gallbladder | Stomach |
| Aorta (Thoracic) | Ovaries | Liver | Lung | Thymus |
| Bone Marrow (Sternum) | Pancreas | Heart | Spinal Cord (Cervical, Mid-Thoracic, and Lumbar) | |
| Brain With Brainstem (Medulla Pons, Cerebella Cortex, and Cerebral Cortex) | | | Lymph Nodes (Mesenteric and Retropharyngeal) | |
| Colon, Cecum, Rectum | Pituitary | Skin | Thyroids (Parathyroid) | Testes with Epididymides |
| Duodenum, Jejunum, Ileum | Prostate | Spleen | Tongue | Trachea |
| Esophagus | Salivary Glands (Mandibular) | | Urinary Bladder | Lesions |
| Eyes (Both with Optic Nerve) | Sciatic Nerve/Adjacent Muscle | | Uterus with Cervix | Kidneys |
| Femur with Bone Marrow (Articular Surface of the Distal End) | | | Vagina | |

**Results:** Only information obtained up to Week 26 (interim sacrifice) was presented this report.

- Mortality and Clinical Signs - No deaths occurred. No remarkable clinical symptoms were attributable to the treatment.
- Food Consumption and Body Weights - There was no difference in mean accumulated body weight change during Weeks 1-26 between SC-58635 treated and control groups. However, some minor fluctuations in mean body weight change were noted in Group 5 ♀ at Week 3 (↑),

Group 4 ♂ Week 26 (↓), and in Group 3 and 7 ♀ at Weeks 4 (↓) and 7 (↓), respectively. Food consumption values were significantly decreased in Group 4 ♂ at Week 15 by 17.4%.

- Rectal Body Temperatures and Respiration Rates - No remarkable differences were noted.
- ECG and - Normal.
- Ophthalmoscopic Examination - No treatment-related effects were seen.
- Clinical Laboratory Pathology - There were some statistically significant changes in hematology and serum chemistry parameters. But these changes were minor and values were within normal reference ranges.
- Gross and Histopathology -



Gross Pathology:

Ogan Weights: Significantly ↑ testes/epidimydes and heart to body weight ratios were noted for Groups 4 and 5 ♂, respectively. Group 3 ♀ had significaltly ↓ liver/gallbladder to body weight ratio.

Microscopic Evaluation: All tissues from Groups 1 and 4 plus the testes and epidymides from Groups 2, 3, and 5 were examined microscopically. There were no treatment-related pathological changes identified.

- PK/TK - Only plasma SC-58635 concentration data of dogs in Groups 2-5 from Days 1 and 178 (Week 26) were included in the current report. Mean PK parameters of SC-58635 on Days 1 and 178 are listed in the following table.

| Day | Dose mg/kg | N | $T_{max}$ (hr) | | $C_{max}$ (μg/ml) | | $AUC_{0-24}$ (μg•hr/ml) | |
|---|---|---|---|---|---|---|---|---|
| | | | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| 1 | 7.5 | 8 | 11.6 | 14.3 | 1.82 | 1.11 | 12.3 | 11 |
| | 12.5 | 8 | 14 | 14.3 | 2.17 | 1.00 | 20.8 | 8.49 |
| | 17.5 | 12 | 14.5 | 9.25 | 2.5 | 1.18 | 26.8 | 10.8 |
| | 25 | 8 | 2.63 | 2.44 | 1.36 | 1.36 | 15.1 | 11.6 |
| 178 | 7.5 | 8 | 14 | 11.5 | 1.15 | 1.6 | 12.6 | 14.4 |
| | 12.5 | 8 | 12.5 | 11.3 | 1.93 | 3.08 | 20.6 | 25.9 |
| | 17.5 | 12 | 14.9 | 11 | 2.79 | 2.58 | 29.7 | 22.3 |
| | 25 | 8 | 3.75 | 1.44 | 0.903 | 0.586 | 9.4 | 4.17 |



There was a sex difference in the plasma concentrations of SC-58635 on Day 1 of dose administration in the 12.5 (bid) and 17.5 (bid) mg/kg dose groups, with male dogs having higher concentrations of the test article than their female counterparts. There were no apparent differences in the plasma concentrations of SC-58635 between ♂ and ♀ dogs on Day 178 of dose administration.

There was a polymorphism (slow & fast clearance) associated with the metabolism of SC-58635 in dogs. The exposure to SC-58635, as measured by AUC, was greater in dogs characterized as having a slow clearance of SC-58635 than those dogs characterized as having a fast clearance of SC-58635. PK parameters analyzed by the rate of clearance are shown in the below table.

| Day | Dose mg/kg | N | $T_{max}$ (hr) | | | | $C_{max}$ (μg/ml) | | | | $AUC_{0-24}$ (μg•hr/ml) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Slow | | Fast | | Slow | | Fast | | Slow | | Fast | |
| | | | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| 1 | 7.5 | 4 | | | | | | | | | | | | |
| | 12.5 | 4 | | | | | | | | | | | | |
| | 17.5 | 6 | | | | | | | | | | | | |
| | 25 | 4 | | | | | | | | | | | | |
| 178 | 7.5 | 4 | | | | | | | | | | | | |
| | 12.5 | 4 | | | | | | | | | | | | |
| | 17.5 | 6 | | | | | | | | | | | | |
| | 25 | 4 | | | | | | | | | | | | |

2.2.2.3. 52-Week Capsule Toxicity Study With SC-58635 In Dogs, Document No.: P30S4425; Date: 03-Mar-1997 (Vol. 1..31-1.32)

Included as an appendix to this report was:
Evaluation Of The SC-58635 Plasma Concentration Data From Week 52 Capsule Toxicity Study With SC-58635 In Dogs, SA4425 (Comparison With 26-Week Data), Document No.: M3097033; Date: 03-Mar-1997

Study Nº: SA4425
Report Nº: M3097033
Study Aim: (1) To identify toxic effects of SC-58635 when administered orally to dogs for at least 52 weeks and reversibility of any toxic effects of the test compound following a 4-week recovery period; (2) To determine the relationship of plasma concentration of test material to the duration of dosing; and (3) To evaluate evidence for sex-related differences in PK parameters.
Compound: SC-58635 (Lot Nº 94K014-A2B)
Vehicle: Empty gelatin capsule
Dosage: 0, 15, 25, and 35 mg/kg/day po for 52 weeks
Animals: 56 & 56 beagle dogs, ~7 months old, weighing kg for ♂ and kg for ♀.

| Main and Recovery Study[a] | | | | Satellite PK Study[b] | | | |
|---|---|---|---|---|---|---|---|
| Group | Dose (mg/kg/dose) | Dose (mg/kg/day) | Nº of Animals/Sex | Group | Dose (mg/kg/dose) | Dose (mg/kg/day) | Nº of Animals/Sex |
| 1 | 0 | 0 | 12 | 6 | 7.5 | 15 | 4 |
| 2 | 7.5 | 15 | 8 | 7 | 12.5 | 25 | 4 |
| 3 | 12.5 | 25 | 8 | | | | |
| 4 | 17.5 | 35 | 12 | | | | |
| 5 | 25.0 | 25 | 8 | | | | |

[a] Dogs in Groups 1-4 & 6-7 received SC-58635 2x/day.
[b] Dogs in Groups 6 & 7 received [$^{14}$C]SC-58635 as 1st daily dose on Day1 and Weeks 26 and 52.

Study Location:

Compliance with GLP/QAU: Yes
Study Date: Dosing started on 9/13/1995 (♂) and 9/20/1995 (♀); interim sacrifice (Groups 1-5, 4/sex/group): 3/14/1996 and 3/21/1996; terminal sacrifice: 9/12 and 9/13/1996 (Groups 1-5, 4/sex/group); recovery sacrifice: 10/17/1996 (Groups 1 and 4, 4/sex/group).
Experimental Design: Dogs were given SC-58635, 0, 7.5x2, 12.5x2, 17.5x2 or 25x1 mg/kg/day in gelatin capsule orally gavage for at least 52 weeks; dosing continued through the day before terminal sacrifice (Weeks 52). Recovery animals were kept without treatment for an additional 4 weeks. Dogs in the companion PK study group received SC-58635 on Days 1, 176 & 358 and received nonradiolabeled SC-58635 on other days during the study. The following observations were conducted.

- Clinical Signs, Mortality, and Moribundity - 2x/day.
- Body weights - Day 1 Pre-Rx, and 1x/week afterwards.
- Food consumption - 1x/week.
- Physical examinations (including rectal temperatures and respiration rates) and ECGs (Leads I, II, and III, aVR, aVL, aVF, $rV_2$, $V_2$, $V_4$, and $V_{10}$) (including heart rates) - 1x before treatment and 1x 1-4 hr postdose during weeks 13, 26, 39 and 52.
- Ophthalmoscopic - pre-Rx and Weeks 26 and 52.

- Clinical Laboratory Evaluations - 1x pre-R and Weeks 13, 26, 39, 52 and 56. The parameters included in the clinical laboratory analysis are listed in the following table.

| HEMATOLOGY | | | | SERUM CHEMISTRY | | |
|---|---|---|---|---|---|---|
| aPTT | WBC | MCH | Hb | ALT | Globulin | Glucose |
| PT | RBC | MCHC | Platelet Count | Albumin | Inorganic Phosphorus | |
| Differential WBC | Ht | MCV | Reticulocyte Count | Albumin/Globulin Ratio | Potassium | Sodium |
| URINALYSIS | | | | Alkaline Phosphatase | Total Bile Acid | |
| Appearance/Color | Occult Blood | | Ketones | AST | Total Bilirubin | |
| Bilirubin | pH | | Urine Potassium | Calcium | Total Cholesterol | |
| Glucose | Protein | | Urine Sodium | γ-Glutamyltransferase (γ-GT) | Total Protein | |
| Microscopic Examination Sediment | | | Total Volume | Chloride | Triglycerides | |
| Urobilinogen | Chloride | | Urine Osmolality | Creatinine | Urea Nitrogen | |

- PK/TK - Blood samples were collected at 0.5, 1, 2, 3, 4, 5, 7, 12, 13, 14, 15, 18 and 24 hr following the ingestion of radiolabeled SC-58635. Urine and fecal samples were collected for 168 hr after each radiolabeled dose approximate 24-hr intervals.
- Necropsies - all animals at the end of the study. The following organs were weighed. Organ-to-terminal-body-weight and organ-to-brain-weight ratios were calculated.

| | | | |
|---|---|---|---|
| Adrenals | Liver with Drained Gallbladder | Prostate | Testes with Epididymides |
| Brain (with Brainstem) | Large Intestine (Cecum and Colon) | Thyroids (with Parathyroid) | |
| Heart | Ovary | Small Intestine (Duodenum, Jejunum, Ileum) | |
| Kidneys | Pituitary | Stomach | Uterus with Cervix |

The following tissues (when present) from each animal were preserved in 10% neutral-buffered formalin. Microscopic evaluations were performed on all tissues from Groups 1 and 4 animals at all scheduled sacrifice.

| | | | | |
|---|---|---|---|---|
| Adrenals | Mammary Gland (♀ Only) | | Gallbladder | Stomach |
| Aorta (Thoracic) | Ovaries | Liver | Lung | Thymus |
| Bone Marrow (Sternum) | Pancreas | Heart | Spinal Cord (Cervical, Mid-Thoracic, and Lumbar) | |
| Brain With Brainstem (Medulla Pons, Cerebella Cortex, and Cerebral Cortex) | | | Lymph Nodes (Mesenteric and Retropharyngeal) | |
| Colon, Cecum, Rectum | Pituitary | Skin | Thyroids (Parathyroid) | Testes with Epididymides |
| Duodenum, Jejunum, Ileum | Prostate | Spleen | Tongue | Trachea |
| Esophagus | Salivary Glands (Mandibular) | | Urinary Bladder | Lesions |
| Eyes (Both with Optic Nerve) | Sciatic Nerve/Adjacent Muscle | | Uterus with Cervix | Kidneys |
| Femur with Bone Marrow (Articular Surface of the Distal End) | | | Vagina | |

**Results:** Only results from terminal and recovery sacrifices were presented in this report.

- Mortality and Clinical Signs - No deaths occurred. No remarkable clinical symptoms were attributable to the treatment. Sporadically, the following abnormal clinical signs were observed: emesis, soft, mucoid or discolored feces and dermological abnormalities.
- Food Consumption and Body Weights - There were no differences in body weights and body weight gains between SC-58635 treated and control dogs. Food consumption values were significantly decreased by17.4% in Group 4 ♂ at Week 15.
- Rectal Body Temperatures and Respiration Rates - No remarkable differences were noted.
- ECG - Normal.
- Ophthalmoscopic Examination - No treatment-related effects were seen.
- Clinical Laboratory Pathology - No significant changes were noted attributable to the treatment.
- Gross and Histopathology - No remarkable pathological changes were attributable to the treatment.
- PK/TK - SC-58635 was absorbed and was systemically available at all doses during the study. The mean PK parameters of SC-58635 on Days 1, 178 and 360 are summarized in the following table. SC-58635 plasma concentrations were similar on Day 178 and 360 indicating that a steady state was maintained during the last 6 months of the 1 year study. There was a sex difference in

the plasma concentrations of SC-58635 on Day 1 of dose administration in the 12.5 (bid) and 17.5 (bid) mg/kg dose groups, with male dogs having higher plasma SC-58635 concentrations than female dogs. There were no apparent sex-related differences in the plasma concentrations of SC-58635 between ♂ and ♀ dogs on Days 178 or 360.

| Day | Dose mg/kg | N | $T_{max}$ (hr) | | $C_{max}$ (μg/ml) | | $AUC_{0-24}$ (μg•hr/ml) | |
|---|---|---|---|---|---|---|---|---|
| | | | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| 1 | 7.5 | 8 | | | | | | |
| | 12.5 | 8 | | | | | | |
| | 17.5 | 12 | | | | | | |
| | 25 | 8 | | | | | | |
| 178 | 7.5 | 8 | | | | | | |
| | 12.5 | 8 | | | | | | |
| | 17.5 | 12 | | | | | | |
| | 25 | 8 | | | | | | |
| 360 | 7.5 | 4 | | | | | | |
| | 12.5 | 4 | | | | | | |
| | 17.5 | 8 | | | | | | |
| | 25 | 4 | | | | | | |



There was a polymorphism (slow & fast clearance) associated with the metabolism of SC-58635 in dogs. The exposure to SC-58635, as measured by AUC, was greater in dogs characterized as having a slow clearance of SC-58635 than those dogs characterized as having a fast clearance of SC-58635. PK parameters analyzed by the rate of clearance are shown in the below table.

| Day | Dose mg/kg | N | $T_{max}$ (hr) | | | | $C_{max}$ (μg/ml) | | | | $AUC_{0-24}$ (μg•hr/ml) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Slow | | Fast | | Slow | | Fast | | Slow | | Fast | |
| | | | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| 1 | 7.5 | 4 | | | | | | | | | | | | |
| | 12.5 | 4 | | | | | | | | | | | | |
| | 17.5 | 6 | | | | | | | | | | | | |
| | 25 | 4 | | | | | | | | | | | | |
| 178 | 7.5 | 4 | | | | | | | | | | | | |
| | 12.5 | 4 | | | | | | | | | | | | |
| | 17.5 | 6 | | | | | | | | | | | | |
| | 25 | 4 | | | | | | | | | | | | |
| 360 | 7.5 | 2 | | | | | | | | | | | | |
| | 12.5 | 2 | | | | | | | | | | | | |
| | 17.5 | 4 | | | | | | | | | | | | |
| | 25 | 2 | | | | | | | | | | | | |

In summary, no treatment caused alterations were identified in all parameters examined; the MTD was not achieved in dog 13-, 26/52-week oral toxicity studies.



## 2.3. CARCINOGENICITY STUDIES

### *2.3.1. RAT STUDY*

2.3.1.1. 104-Week Oral Gavage Carcinogenicity Study In Rats With SC-58635 (SA4367), Document No: P20S4367; Date: 19-Dec-1997 (Vol. 1.42 - 1.50)

Included as an appendix to this report is:
Pharmacokinetic Support For The 104-Week Oral Gavage Carcinogenicity Study In Rats With SC-58635 (SA4367), Document No.: M3097146; Date: 10- Dec-1997 (Vol. 1.50)

Study Nº: SA4367
Report Nº: P20S4367

Study Aims: To determine the carcinogenic potential of SC-58635 to rats by oral gavage for at least 104 weeks.

Compound: SC-58635 suspended in 0.5% Methylcellulose (400 cps) + 0.1% polysorbate 80 (Tween® 80) + distilled water

| Lot Nº | Weeks Used | Expiration Date |
|---|---|---|
| 94K014-A4A | 1- 15 | Not Indicated. |
| 94K014-A2B | 15- 27 | August 1995 |
| 94K031-A3A | 27- 51 | November 1995 |
| 95K010-A1A | 52- 67 | May 1997 |
| 94K031-A2A | 67- 92 | November 1997 |
| 95K010-A1A | 92- 105 | May 1998 |



Vehicle Control: 0.5% methylcellulose (w/v) and 0.1% polysorbate 80 in distilled water.

Dose & Route: 0, 20, 80, and 400 mg/10 ml/kg/day po by gavage; As of Week 18, the dose level for the high-dose females was reduced to 200 mg/kg/day; as of Week 78, the dose levels for the low- and mid-dose females were reduced to 5 and 10 mg/kg/day, respectively, and for the high-dose males to 200 mg/kg/day.

Animals: Sprague-Dawley rats of the Crl:CD®BR strain

, ~6 weeks of age, weighing 178-273 g for ♂ and 127-197 g.

Study Site:

In-Life Observation: 3/16/95 - 3/19/97;
Interim Sacrifice: 3/15/96 (Week 53)
Terminal Sacrifice: 3/14-19/97



GLP/QAC Compliance: Yes

Study Design: Rats were given SC-58635 in 0.5% methylcellulose (w/v) + 0.1% polysorbate 80 as a suspension once daily by oral gavage. Dose levels and group assignments are listed in the following table.

| Group | Dose mg/kg/day | | | | | Nº of Animals | | Animal Numbers | |
|---|---|---|---|---|---|---|---|---|---|
| | Wk 1-17 | Wk 18-77 | | Wk 78-104 | | | | | |
| | ♂ & ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| MAIN STUDY ANIMALS | | | | | | | | | |
| 1 (Control) | 0 | 0 | 0 | 0 | 0 | 80 | 80 | B57665 - B57744 | B57745 - B57824 |
| 2 (Low) | 20 | 20 | 20 | 20 | 5 | 80 | 80 | B57825 - B57904 | B57905 - B57984 |
| 3 (Mid) | 80 | 80 | 80 | 80 | 10 | 80 | 80 | B57985 - B58064 | B58065 - B58144 |
| 4 (High) | 400 | 400 | 200 | 200 | 200 | 80 | 80 | B58145 - B58224 | B58225 - B58304 |
| SATELLITE ANIMALS | | | | | | | | | |
| 5 (Low) | 20 | 20 | 20 | 20 | 5 | 26 | 26 | B58305 - B58330 | B58331 - B58356 |
| 6 (Mid) | 80 | 80 | 80 | 80 | 10 | 26 | 26 | B58357 - B58382 | B58383 - B58408 |
| 7 (High) | 400 | 400 | 200 | 200 | 200 | 26 | 26 | B58409 - B58434 | B58435 - B58460 |

* The last ten animals/sex/group were designated for the Week 53 interim sacrifice.

The doses selected in this study were based on the results of a 4-week oral gavage study at doses of 0, 20, 80, 400 and 600 mg/kg in which it was shown that absorption of SC-58635 attained a plateau at dosages ≥400 mg/kg/day for ♂ rats ($AUC_{0-24}$ for 400 and 600 mg/kg ♂: 195.9 and 97.6 on Day 1 and 60.7 and 58.2 μg•hr/ml on Day 26, respectively) and deaths were seen at 600 mg/kg/day for ♀ rats. The following parameters were monitored:

- Mortality and Clinical Signs - 2x/day.
- Physical Examination - Weeks 1-52, 1x/4 weeks; Weeks 53-104, 1x/2 weeks.
- Body Weight and Food Consumption - 1x/pre-R; Weeks 1-26, 1x/week; Weeks 27-52, 1x/2 weeks; 1x/4 weeks thereafter.
- Ophthalmoscopic Examinations - 1x/pre-R.

- Clinical Pathology - Blood samples were collected at Weeks 53 (interim-sacrifice animals), 79 (all high-dose Main Study and Satellite ♀), and 104 (all surviving Main Study and Satellite animals) for hematology and serum chemistry analyses. Urine specimens were obtained from animals in individual urine collection cages. The specimens for routine urinalysis were obtained following 4 hours (±15 min) of collection. Collections continued for a total of 22 hours (±15 min) and the total volume was recorded after the final collection. The following parameters were determined:

| HEMATOLOGY | | SERUM CHEMISTRY | |
|---|---|---|---|
| aPTT | MCH | ALT | Inorganic Phosphorus |
| PT | MCHC | Albumin | Potassium |
| Differential Count and Cell Morphology | MCV | Albumin/Globulin Ratio | Protein Electrophoresis |
| WBC | Mean Platelet Volume | Alkaline Phosphatase | Sodium |
| RBC | Platelet Count | AST | Sorbitol Dehydrogenase |
| Ht | Reticulocyte Count | Calcium | Total Bilirubin |
| Hb | | Chloride | Total Cholesterol |
| ROUTINE URINALYSIS | | Creatinine | Total Protein |
| Appearance/Color | Occult Blood | Globulin | Triglycerides |
| Bilirubin | pH | Glucose | Urea Nitrogen |
| Glucose | Protein | URINE CHEMISTRY | |
| Ketones | Urobilinogen | Urine Sodium | Urine Osmolality |
| Microscopic Sediment | | Urine Potassium | Total Volume |

- PK/TK - Day 1, Weeks 26, 52, and 78. Whole blood was collected from the satellite study animals (3 /sex/group/time point) at 0.5, 1, 2, 3, 4, 6, 8, and 24 hours after dose administration. The plasma samples were stored at approximately -20°C until shipment to the Sponsor on dry ice. At Week 53, kidneys were collected from the Week 53 interim-sacrifice animals, frozen in liquid nitrogen and stored at -70°C until shipment. Analyses of the plasma, serum or tissue SC-58635 concentrations was performed by The concentrations of SC-58635 in plasma and serum were determined using a validated procedure with an assay sensitivity of 0.0250 μg SC-58635/ml for a 0.300 ml sample. The concentrations of SC-58635 in kidney were determined using a non-validated procedure with an assay range of μg SC-58635/g tissue.
- Gross and Histopathology - Necropsies were performed on animals sacrificed at moribund and the scheduled sacrificed animals (Weeks 53 and 104/105). The following organs from animals sacrificed at Week 53 were weighed at necropsy. Paired organs were weighed together. Organ-to-terminal-body weight and organ-to-brain weight ratios were determined.

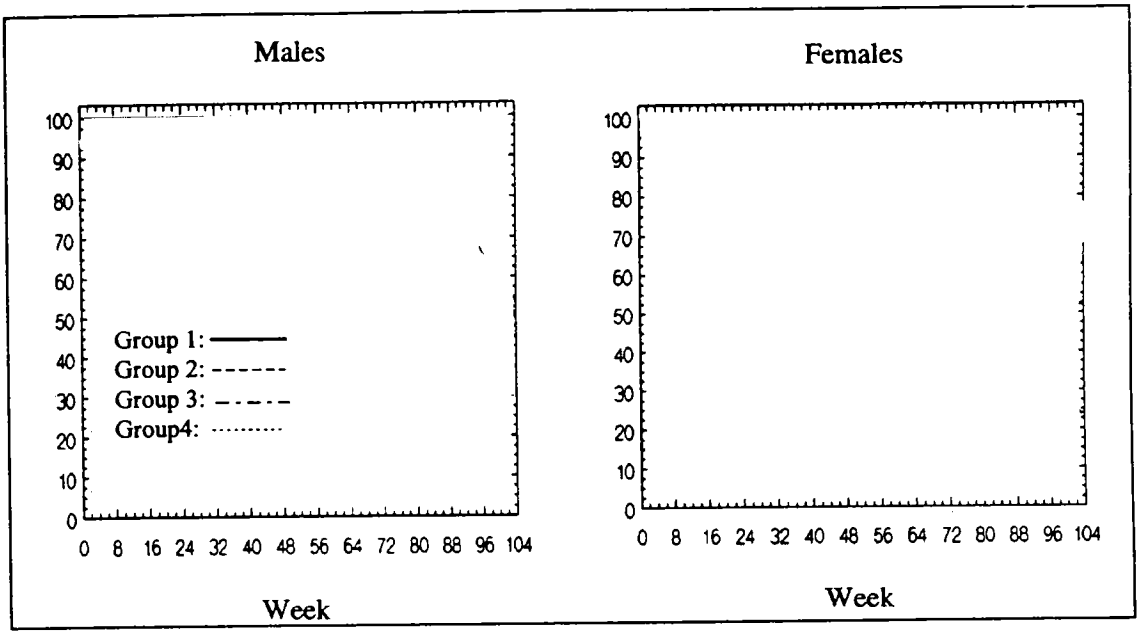
| | | | | | | |
|---|---|---|---|---|---|---|
| adrenals | ovaries | lung | stomach (empty) | thyroid with parathyroids (postfixation) | | |
| brain (with brainstem) | heart | pituitary (postfixation) | testes with epididymides | uterus | | |
| cecum (empty) | kidneys | prostate | thymus | colon (empty) | liver | spleen |

The following tissues (when present) from all Main Study animals and selected Satellite animals were preserved in 10% neutral-buffered formalin. Microscopic examinations were performed on the preserved tissues from all animals in the Main Study and all Satellite animals that died after 4 February 1997 (Day 6 of Week 99).

| | | | | |
|---|---|---|---|---|
| Adrenals (Both) | Harderian Gland | Pancreas | Testes with Epididymides (Both) | |
| Aorta (Thoracic) | Heart | Pituitary | Thigh Musculature | |
| Bone Marrow (Femur and Sternum) | Kidneys (Both) | Prostate | Thymus | Tongue |
| Brain with Brainstem (Medulla/Pons, Cerebellar Cortex, and Cerebral Cortex) | | Salivary Glands (Mandibular) | Thyroid (Parathyroids) | |
| Colon, Cecum, Rectum | Liver | Sciatic Nerve | Trachea | Urinary Bladder |
| Duodenum, Jejunum, Ileum | Lung (with Bronchi) | Seminal Vesicle | Ovaries (Both) | Stomach |
| Esophagus | Mammary Gland with Skin | Spinal Cord (Cervical. Mid-Thoracic, and Lumbar) | Gross Lesions | Spleen |
| Eyes (Both with Optic Nerve) | Mesenteric Lymph Node | Femur Including Articular Surface | Uterus with Vagina and Cervix | |

Results:

- Mortality and Clinical Signs - Treatment-related deaths increased with dose and occurred in the mid- and high-dose ♂ and all treated female groups (Group 2: 4♀; Group 3: 4♂ & 20 ♀; Group 4: 19♂ & 31♀) with confirmed histopathological lesions of gastrointestinal necrosis with inflammation and associated peritonitis. The major clinical observations included higher frequencies of hypoactivity, few feces, cold to touch and dyspnea in the treated groups.




Statistical analyses of survival rates revealed a significant negative trend ($p<0.01$) in survival in both sexes; the mortality rates of the high-dose males and all treated female groups were significantly higher than control. Adjusted survival for ♂ and ♀ was plotted as proportion surviving versus time as shown in the above figures. The life-time mortality, including the survival data of the satellite groups, for each group is presented in the following table.

| | Life-Time Mortality | | | |
|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 |
| ♂ | 39/80 | 50/106 | 65/106 | 73/106 |
| ♀ | 37/80 | 77/106 | 77/106 | 60/106[a] |

[a] Group 4 ♀ either died or were sacrificed during Week 79.

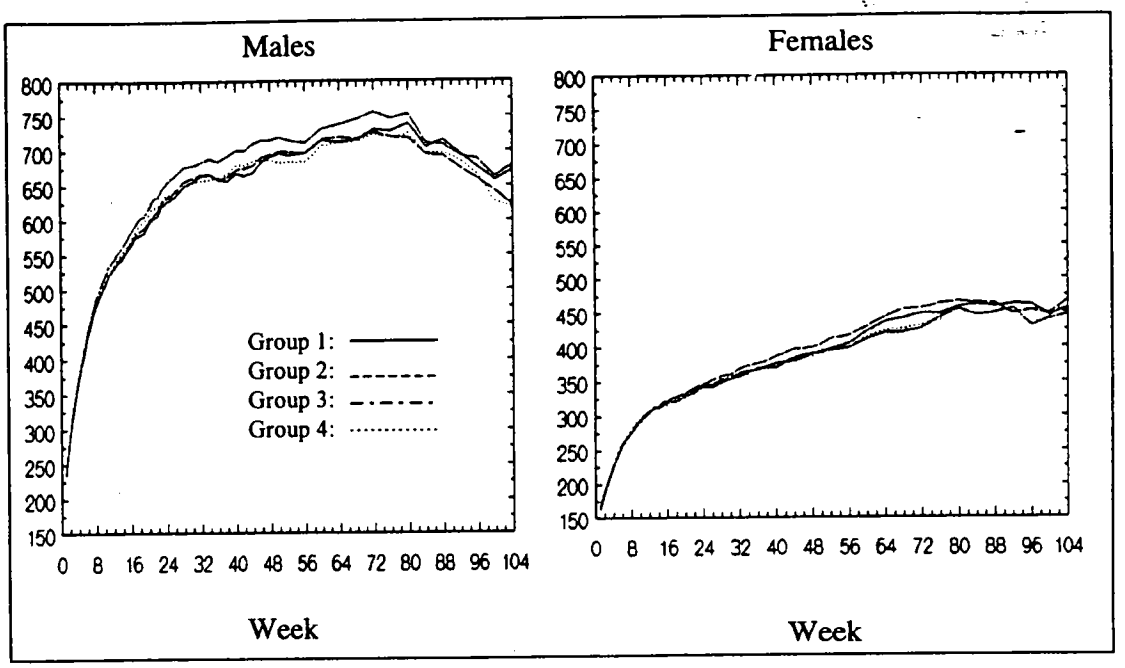


The incidence of deaths for the main study animals occurred at various stages during the study is listed in the following table. Due to excessive toxicity, high dose females were sacrificed at Week 79.

| Group | 1 | | 2 | | 3 | | 4 | |
|---|---|---|---|---|---|---|---|---|
| | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| **UNSCHEDULED DEATHS** | | | | | | | | |
| Weeks 1-52 | 3 | 1 | 4 | 6 | 3 | 16 | 10 | 25 |
| Weeks 53-78 | 12 | 3 | 11 | 15 | 14 | 20 | 13 | 20 |
| Weeks 79-105 | 24 | 33 | 23 | 38 | 31 | 22 | 26 | 0 |
| Total Deaths | 39 | 37 | 38 | 59 | 48 | 58 | 49 | 45 |
| **SCHEDULED SACRIFICE** | | | | | | | | |
| Interim Kill (Week 53) | 5 | 5 | 5 | 5 | 4 | 4 | 4 | 3 |
| Terminal Kill | 36 | 38 | 37 | 16 | 28 | 18 | 27 | 32[a] |
| Total | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 |

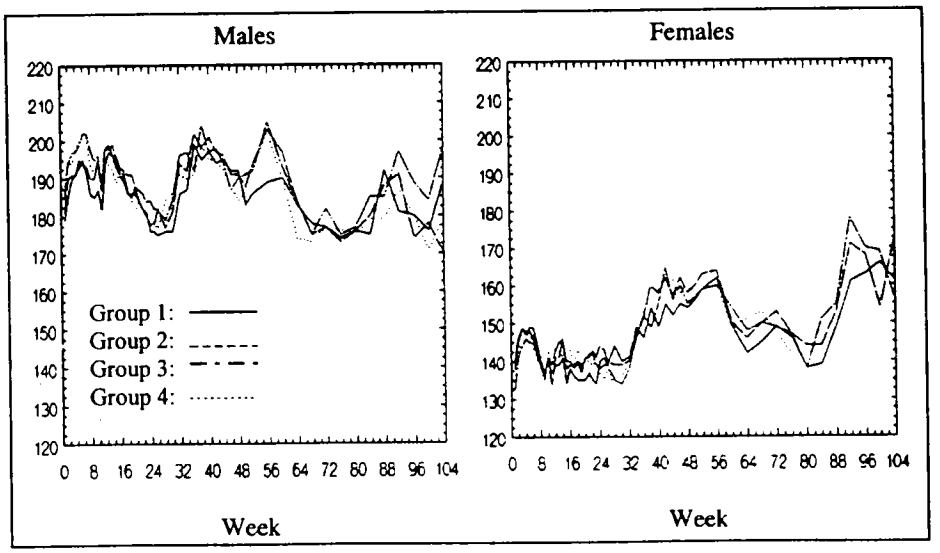
[a] Killed Week 79.

Body Weight and Food Consumption - Mean body weights for each group during the study are illustrated in the following two figures. Group 3 ♂ had significantly higher body weight values




(↑4-5%) during Weeks 18-46. Sporadic significant differences (↑ or ↓) in mean body weight change values were noted in SC-58635 treated groups when compared to the controls. Group 3 ♂ (Weeks 1-18, ↑7.9%) and Group 2 ♀ (Weeks 18-52, ↑23%) had higher interval total body weight change values. Significantly lower interval total body weight change values (↓20%) were observed in Group 4 ♂ at Weeks 18-52.

The mean food consumption values for the Group 3 and 4 ♂ over the first 12 weeks of treatment were higher than control (~5%). Comparable mean food consumption values of both sexes were observed for the rest of study. Interval total food consumption values for Weeks 1-18, 18-53, 1-78, and 1-104 were similar for all groups with the exception of a significantly higher mean value for the Group 3 ♂ at Weeks 1-18 (↑35.8%). Mean food consumption for each group during 2-year study are shown in the following figures.



- Clinical Pathology -
  Hematology: No remarkable findings were identified during Weeks 53 and 79 analyses. Significantly ↑ WBC counts were noted all treated ♂ at Week 105 with values of $12.1x10^3/\mu l$, $14.7x10^3/\mu l$, $14.1x10^3/\mu l$, and $16x10^3/\mu l$ for Groups 1, 2, 3, and 4, respectively. In addition, Group 2 ♂ had ↓ in RBC (6.51 vs $8.19x10^6/\mu l$ in controls), Hb (11.5 vs 13.6 g/dl in controls) and Hct (33.9 vs 39.4% in controls) and an ↑ in the absolute reticulocyte count (0.23 vs $0.12x10^6/\mu l$ in controls).

  Clinical Chemistry: Slight ↑ in β-globulin in Group 2-4 ♂ and α-2-globulin in Group 3 females were noted at Week 105. These changes were of low magnitude and not biologically significant. Significantly ↑ mean values were observed for inorganic phosphorus (6.6 vs 5.9 mg/dl), sodium (146 vs 145 meq/l), and chloride (102 vs 98 meg/l) in Group 3 ♀ and potassium (5.2-5.3 vs 4.8 meq/l) in Group 2 and 3 ♀ at Week 105. These values were within published biological ranges and might not have biological impacts.

  Urinalysis: There were no significant findings between the groups at Weeks 53 and 79 and 105.
- PK/TK - SC-58635 was absorbed systemically. Female rats had higher $C_{max}$ and AUC values than ♂ rats. Mean AUC and $C_{max}$ values for each group on Days 1, 180, 359, and 541 are summarized in the following table. The exposure of the low and mid dose ♀ rats to SC-58635 was 2x of the values observed in ♂ rats. The exposure to SC-58635 in the high dose female rats, as measured by $AUC_{0-24}$ was ~20 and 10x of that observed in humans at the doses of 200 and 400 mg/day, respectively. The exposure of the high dose ♂ rats to SC-58635 was ~10 and 5x of that observed in humans at 200 and 400 mg/day, respectively. At 104 Weeks sacrifice, serum SC-58635 concentrations were 0.321, 3.30 and 5.52 μg/ml for low, mid and high ♂ rats, respectively and were 3.08 and 1.24 μg/ml for the low and mid dose female rats, respectively. At the Week 53 interim sacrifice, kidney concentrations of SC-58635 were 3.37, 9.53 and 15.1 μg/g for ♂ rats and were 4.22, 13.0 and 12.8 μg/g for ♀ rats in the low, mid and high dose groups, respectively. These values were approximately 2-3x times higher than corresponding $C_{max}$ concentrations of SC-58635 in plasma, indicating that the test article was distributed to the kidney.

| Group | Dose mg/kg/day | PK Parameter | Day 1 (Wk1) | | Day 180 (Wk 26) | | Day 359 (Wk 52) | | Day 541 (Wk 78) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| Low | 20 | $C_{max}$ (μg/ml) | | | | | | | | |
| | 5 | | | | | | | | | |
| Mid | 80 | | 3.42 | 5.63 | 3.09 | 7.46 | 2.88 | 7.44 | 0.893 | 2.00 |
| | 10 | | | | | | | | | |
| High | 400 | | | | | | | | | |
| | 200 | | | | | | | | | |
| Low | 20 | $AUC_{0-24}$ (μg•hr/ml) | | | | | | | | |
| | 5 | | | | | | | | | |
| Mid | 80 | | 42.6 | 81.2 | 39.0 | 111 | 38.2 | 114 | 11.6 | 27.7 |
| | 10 | | | | | | | | | |
| High | 400 | | | | | | | | | |
| | 200 | | | | | | | | | |

- Gross and Histopathology -
  Organ Weight: Organ weights were only recorded at interim Week 53 sacrifice. Significant increases in the kindey/brain (↑ 13.1%) and liver/body (↑ 12.9%) weight ratios were noted in Group 4 ♂. However, there were no corresponding histopathological lesions found during microscopic evaluations.

  Non-neoplastic Histopathological Findings:

**Unscheduled Deaths**

Dose-dependent GI necrosis/perforation (mainly in the jejunum) with associated abdominal inflammation and pyelonephritis were the only major treatment-related histomorphologic finding in unscheduled deaths during the study. The common causes of fatality are listed as followings:

| Most Common Causes of Death | Group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | | 2 | | 3 | | 4 | |
| | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| Pituitary Neoplasm | 13 | 20 | 13 | 37 | 12 | 20 | 7 | 4 |
| GI Necrosis/Inflammation | 0 | 0 | 0 | 4 | 4 | 20 | 19 | 31 |
| Mammary Neoplasm (s) | 1 | 9 | 1 | 9 | 0 | 12 | 0 | 1 |
| Chronic Progressive Nephropathy | 4 | 1 | 3 | 2 | 5 | 0 | 5 | 2 |
| Pyelonephritis | 0 | 0 | 2 | 0 | 2 | 0 | 4 | 0 |
| Lymphoma | 2 | 1 | 4 | 0 | 1 | 0 | 1 | 0 |



Inflammation of the serosal surface of abdominal viscera including the capsule of the spleen, liver, lung, heart (♀ only), pancreas (♀ only), kidneys, urinary bladder, and sex-organs was commonly observed as a secondary effect of test article-related necrosis in the gastrointestinal tract. A low but statistically significant increase in the incidence of pyelonephritis was identified in ♂ rats only (2/38, 5/49, 6/49 in Groups 2, 3, 4, respectively). In addition, dose-dependent pathological changes in the thymus with characteristics of lymphoid depletion, chronic active inflammation and necrosis were noted for ♀ but not ♂. These kind of alterations have been observed in notably stressed rats prior to death or animals treated with compounds possessing immunotoxic properties. Observations in this study were not likely caused by treatment-induced immunotoxicity as there were no similar findings seen in the scheduled sacrificed animals. Incidence of GI pathological changes for each group are listed in the following table.

| Microscopic Findings | Unscheduled Deaths | Group 2 | | Group 3 | | Group 4 | |
|---|---|---|---|---|---|---|---|
| | | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| GI Necrosis/Inflammation | Weeks 1-52 | | 2 | | 13 | 2 | 19 |
| Abdominal Inflammation | | | | 1 | | 1 | 3 |
| GI Necrosis/Inflammation | Weeks 53-78 | | 1 | 2 | 7 | 10 | 12 |
| GI Necrosis/Inflammation | Weeks 79-105 | | 1 | 2 (1)[a] | (1) | 7 (1) | |

[a] Numbers in the parentheses represent data from the Satellite animals.



**Interim Sacrifice**

No treatment-related microscopic findings were identified in the sections from interim sacrificed rats (Week 53).

**Terminal Sacrifice**

For rats sacrificed at termination of study, test article-related findings of small intestinal necrosis and inflammation were present in the jejunum of one Group 3 male and in two Group 4 males. In addition, small intestinal necrosis with fibrosis and inflammation were present in two Group 2 females.

The incidence of major non-neoplastic findings (statistically significant at 5 or 1%) for each group, including data from the Satellite animals, during entire period of study are summarized in the following table.

| Non-neoplastic Findings | Incidence Rates | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Group 1 | | Group 2 | | Group 3 | | Group 4 | |
| | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| Duodenum - Congestion | 0/80 | 0/80 | 0/95 | 4/90 | 1/92 | 16/90** | 5/86** | 22/80** |
| Duodenum - Serosa, Chronic Active Inflammation | 0/80 | 1/80 | 0/95 | 2/90 | 6/92** | 5/90 | 16/86** | 6/79* |
| Jejunum - Congestion | 0/80 | 1/80 | 0/94 | 3/90 | 1/90 | 12/90** | 4/86** | 17/79** |
| Jejunum - Necrosis | 0/80 | 0/80 | 0/94 | 4/90 | 4/90** | 18/90** | 13/86** | 28/79** |
| Jejunum - Serosa, Chronic Active Inflammation | 0/80 | 0/80 | 1/94 | 1/90 | 10/90** | 4/90** | 18/86** | 5/79*§ |
| Ileum - Congestion | 0/80 | 1/80 | 0/95 | 1/90 | 0/92 | 4/90 | 3/86** | 8/79** |
| Ileum - Necrosis | 0/80 | 0/80 | 0/95 | 7/90* | 0/92 | 15/90** | 6/86** | 21/79*§ |
| Ileum - Serosa, Chronic Active Inflammation | 0/80 | 0/80 | 1/95 | 7/90* | 6/92** | 15/90** | 19/86** | 21/79** |
| Stomach, Nonglandular - Hyperplasia | 3/79 | 5/80 | 8/95 | 10/90 | 7/92 | 6/89 | 9/86 | 8/79 |
| Stomach, Nonglandular - Serosa, Chronic Active Inflammation | 0/79 | 0/80 | 0/95 | 1/90 | 3/92* | 4/89* | 9/86** | 19/79** |
| Stomach, Nonglandular - Necrosis | 0/79 | 0/80 | 0/95 | 0/90 | 1/92 | 3/89* | 3/86* | 6/79** |
| Stomach, Glandular - Erosion | 8/79 | 11/80 | 9/95 | 14/90 | 20/92* | 16/90 | 20/86** | 2/79 |
| Stomach, Glandular - Serosa, Chronic Active Inflammation | 0/79 | 0/80 | 0/95 | 2/90 | 5/92** | 12/90** | 12/86** | 16/79** |
| Colon - Serosa, Chronic Active Inflammation | 0/80 | 0/80 | 1/95 | 3/90 | 8/92** | 11/90** | 15/86** | 20/80** |
| Cecum - Edema | | 0/80 | | 2/90 | | 3/90 | | 4/80* |
| Cecum - Congestion | 0/80 | 1/80 | 5/95* | 6/90 | 5/92* | 3/90 | 7/85** | 4/80 |
| Cecum - Necrosis | 0/80 | 0/80 | 4/95 | 5/90 | 5/92* | 3/90 | 6/85* | 7/80* |
| Cecum - Serosa, Chronic Active Inflammation | 0/80 | 0/80 | 1/95 | 2/90 | 4/92* | 13/90** | 14/85** | 22/80** |
| Rectum - Serosa, Chronic Active Inflammation | | 0/80 | | 0/90 | | 1/88 | | 4/80** |
| Kidney - Capsule, Chronic Active Inflammation | 1/80 | 0/80 | 0/95 | 1/90 | 1/92 | 7/90** | 8/86** | 15/80** |
| Kidney - Pyelonephritis | 0/80 | | 4/95 | | 5/92* | | 6/86* | |
| Lung - Congestion | 30/80 | 20/80 | 40/95 | 44/90** | 41/92 | 42/90** | 45/86* | 39/80** |
| Lung - Leukocytosis | 5/80 | 4/80 | 5/95 | 6/90 | 10/92 | 13/90* | 22/86** | 14/80** |
| Lung - Diffuse Pneumonitis | 0/80 | | 0/95 | | 6/92** | | 3/86* | |
| Lung - Pleura, Chronic Active Inflammation | | 0/80 | | 1/90 | | 4/90* | | 6/80** |
| Lung - Thrombosis | 1/80 | | 0/95 | | 2/92 | | 4/86* | |
| Heart - Epicardium, Chronic Active Inflammation | | 0/80 | | 3/90 | | 6/90** | | 7/80** |
| Spleen - Hyperplasia, Myeloid | 0/80 | 0/80 | 1/95 | 3/90 | 3/92* | 1/89 | 7/86** | 9/80** |
| Spleen - Capsule, Chronic Active Inflammation | 0/80 | 0/80 | 1/95 | 1/90 | 9/92** | 16/89** | 19/86** | 24/80** |
| Liver - Capsule, Chronic Active Inflammation | 0/80 | 0/80 | 2/95 | 3/90 | 8/92** | 18/90** | 20/86** | 28/80** |
| Pancreas - Inflammation, Chronic Active | 0/80 | 0/80 | 3/95 | 2/88 | 8/92** | 20/89** | 24/86** | 31/80** |
| Mesenteric Lymph Node - Lymphangiectasis | 1/80 | | 5/93 | | 10/90** | | 5/85* | |
| Mesenteric Lymph Node - Hyperplasia, Lymphoreticular | 0/80 | 0/79 | 3/93 | 4/89 | 8/90** | 8/90** | 15/85** | 20/80** |
| Mesenteric Lymph Node - Inflammation, Chronic Active | 0/80 | 0/79 | 1/93 | 3/89 | 4/90* | 11/90** | 13/85** | 14/80** |
| Testis - Tunics, Chronic Active Inflammation | 0/80 | | 1/95 | | 6/92** | | 7/86** | |
| Epididymis - Inflammation, Chronic Active | 0/80 | | 1/95 | | 1/92 | | 9/86** | |
| Seminal Vesicle - Inflammation, Chronic Active | 9/80 | | 9/95 | | 13/91 | | 24/86** | |
| Urinary Bladder - Serosa, Chronic Active Inflammation | 1/80 | 0/78 | 1/95 | 1/89 | 5/92* | 12/88** | 15/86** | 17/80** |
| Marrow, Sternum - Hyperplasia, Myeloid | 21/80 | | 30/95 | | 42/92** | | 43/86** | |
| Marrow, Femur - Hyperplasia, Myeloid | 21/79 | | 29/95 | | 41/90** | | 43/86** | |
| Ovary - Inflammation, Chronic Active | | 0/79 | | 1/90 | | 15/90** | | 17/80** |
| Uterus - Serosa, Chronic Active Inflammation | | 0/79 | | 3/90 | | 10/90** | | 9/80** |
| Cervix - Serosa, Chronic Active Inflammation | | 0/79 | | 0/90 | | 2/89* | | 5/78** |
| Thymus - Congestion | 15/71 | 10/69 | 23/89 | 26/79** | 22/83 | 29/81** | 26/75* | 23/70** |
| Thymus - Depletion, Lymphoid | 7/71 | 2/69 | 10/89 | 5/81 | 6/83 | 15/81** | 13/75 | 20/70** |
| Thymus - Inflammation, Chronic Active | | 0/69 | | 1/81 | | 2/81 | | 3/70* |
| Thymus - Necrosis | | 1/69 | | 0/81 | | 3/81 | | 5/69* |
| Brain w/ Stem - Congestion | 16/80 | 9/80 | 16/95 | 13/90 | 14/92 | 21/90* | 24/86 | 20/80** |

*p<0.05; **p<0.01

Neoplastic Findings: There were no statistical differences in the incidence of neoplastic lesions between controls and animals treated with SC-58635.

Incidence of major neoplastic findings for each group (including data from the Satellite animals) is listed in the following table.

| Neoplastic Findings | Incidence Rates | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Group 1 | | Group 2 | | Group 3 | | Group 4 | |
| | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| Adrenal, Medulla - Primary Benign Pheochromocytoma | 5/80 | 0/78 | 7/95 | 0/89 | 6/92 | 1/89 | 7/86 | 0/78 |
| Brain w/ Stem - Primary Benign Granular Cell Tumor | 0/80 | | 3/95 | | 1/92 | | 0/86 | |
| Pituitary - Primary Benign Adenoma | 43/80 | 55/80 | 50/95 | 65/90 | 47/90 | 48/90 | 36/86 | 29/80 |
| Pituitary - Primary Malignant Carcinoma | 0/80 | 9/80 | 1/95 | 9/90 | 1/95 | 4/90 | 2/86 | 2/80 |
| Pancreas - Primary Benign Islet Cell Adenoma | 5/80 | 5/80 | 9/95 | 4/88 | 8/92 | 2/89 | 6/86 | 1/80 |
| Pancreas - Primary Malignant Islet Cell Carcinoma | 3/80 | | 3/95 | | 7/92 | | 1/86 | |
| Testes - Primary Benign Interstitial Cell Tumor | 1/80 | | 3/95 | | 1/92 | | 4/86 | |
| Hematoneoplasia - Primary Malignant Lymphoma | 2/80 | 2/80 | 6/95 | 3/90 | 1/92 | 1/90 | 1/86 | 0/80 |
| Thyroid - Primary Benign "C' Cell Adenoma | 8/80 | 10/80 | 12/94 | 10/90 | 10/91 | 7/90 | 8/86 | 4/80 |
| Uterus - Primary Benign Endometrial Stromal Polyps | | 0/79 | | 3/90 | | 2/90 | | 0/80 |
| Uterus - Endometrial Stromal Polyps/Carcinoma | | 1/79 | | 3/90 | | 2/90 | | 0/80 |
| Mammary - Primary Benign Fibroadenoma | 2/80 | 40/78 | 3/95 | 32/80 | 2/92 | 29/80 | 3/86 | 9/79 |
| Mammary - Primary Malignant Carcinoma | 1/80 | 19/78 | 1/95 | 13/80 | 0/92 | 12/80 | 0/86 | 5/79 |
| Mammary - Primary Benign Fibroadenoma and/or Primary Malignant Carcinoma | | 46/78 | | 41/80 | | 36/80 | | 13/79 |

Based on presented findings, administration of SC-58635 to rats for 104 weeks did not cause an increase in the incidence for all examined tumors. It did induce GI lesions (necrosis/perforation/inflammation with secondary peritonitis) at all does levels for ♀ and >20 mg/kg/day for ♂. In addition, increased incidence of pyelonephritis were noted in treated male. The NOAEL for ♂ rats was 20 mg/kg. The NOAEL for ♀ rats could not be established under current study since treatment-related deaths occurred at all tested doses.

*2.3.2. MOUSE STUDY*

2.3.2.1. Dietary Admix Carcinogenicity Study Of SC-58635 In The Mouse (SA4452), Document No: P30S4452; Date: 05- Mar- 1998 (Vol. 1.33 -1.41)

Included as an appendix to this report is:
Evaluation Of Plasma SC-58635 Concentration Data For The Dietary Admix Carcinogenicity Study Of SC-58635 In The Mouse (SA4452), Document No.: M3097237; Date: 10-Mar-1998 (Vol. 1.38)

Study Nº: 95107/SA4452
Report Nº: P30S4452
Study Aims: To determine the carcinogenic potential of SC-58635 when administered ad libitum in the diet to mice for at least 104 weeks.
Compound: SC-58635, Lot Nº GDS-4695-042
Dose and Route: 0, 25, 50, and 75 mg/kg/day in the diet for ♂ and 0, 50, 100, and 150 mg/kg/day in the diet for ♀.
Animal: Charles River CD-1 mice
weeks of age, weighing g, 90/sex/group for the toxicology, 65/sex/group for the PK study.

Study Site:
In-Life:
Tissue Processing & Microscopic Examinations:

Plasma PK Assessment:
In-Life Observation: 11/28/95 - 12/01-05 & 08/97
Interim Sacrifice: 11/25-26/96 (Days 364 & 365)
Terminal Sacrifice: 12/01-05 & 08/97 (Days 735, 736, 737, 738, 739, and 742)

GLP/QAC Compliance: Yes

Study Design: The dosages and animal grouping are shown in the following table.

| Group | Dose (mg/kg) | | | | | Animals/Sex/ Group | Animals/Sex | | |
|---|---|---|---|---|---|---|---|---|---|
| | ♂ | | ♀ | | | | Interim Sacrifice | Terminal Sacrifice | |
| | Wk1-18 | Wk 19-104 | Wk1-18 | Wk19-22 | Wk 23-104 | | Week 53 | Week 80 | Week 105-106 |
| **TOXICOLOGY ANIMALS** | | | | | | | | | |
| N | 0[a] | 0 | 0 | 0 | 0 | 90 | 10 | - | All Survivors |
| 1 | 25 | 12.5 | 50 | 25 | 25 | 90[b] | 10 | - | All Survivors |
| 2 | 50 | 25 | 100 | 50 | 50 | 90[b] | 10 | - | All Survivors |
| 3 | 75 | 37.5 | 150 | 75 | 150 | 90 | 10 | All Survivors | - |
| **PHARMACOKINETIC ANIMALS** | | | | | | | | | |
| 4 | 0 | 0 | 0 | 0 | 0 | 20 | - | All Survivors | - |
| 5 | 25 | 12.5 | 50 | 25 | 25 | 65 | - | - | - |
| 6 | 50 | 25 | 100 | 50 | 50 | 65 | - | - | - |
| 7 | 75 | 37.5 | 150 | 75 | 150 | 65 | - | All Survivors | - |

[a] Control animals received the basal diet only.

[b] Week 92, surviving Pharmacokinetics males in Groups 5 (4♂ & 6♀) and 6 (4♂ & 4♀) were transferred to Toxicology Groups 1 and 2, respectively.

The following observations were conducted.

- Clinical Signs, Mortality and Moribundity - 2x/day.
- Detailed Observations - 1x/week for visible and/or palpable masses.
- Body Weights and Food Consumption - 2x/pre-R; 1x/week 1st 26 weeks (6 months), 1x/2 weeks for the 2nd 6 months, and 1x/4 weeks thereafter.
- Clinical Pathology - Weeks 53, 80, and 105 to 106. Blood was collected from randomly selected 10 animals/sex/group in the Toxicology groups and from all animals in the control PK group (Week 80 only). The following listed variables were determined from the plasma. Parameters in Priority List 1 were analyzed first followed by those in Priority List 2. Blood smears were prepared for all animals sacrificed at Week 53 but not examined.

| PRIORITY 1 | | PRIORITY 2 | | |
|---|---|---|---|---|
| ALT | Total Protein | AST | Glucose | Total Bile Acids |
| Albumin | Alkaline Phosphatase | Chloride | Potassium | Total Bilirubin |
| BUN | Inorganic Phosphorus | Cholesterol | Sodium | Triglycerides |
| Creatinine | Calcium | Globulin (Calculated Value) | Sorbitol Dehydrogenase | |

- Test Article Bioavailability - Days 3-4 and Weeks 19, 52, and 78. Blood was collected at approximately 2400, 0600, 0900, and 1500 hours from three animals/sex/group in Groups 5, 6, and 7 and at 0900 hours from three animals/sex in Group 4.
- Necropsy - Unscheduled deaths, scheduled interim (Week 53, toxicology study animals, 10/sex/group) and terminal sacrifices (Weeks 105 and 106: toxicology animals, Groups N, 1, 2, 3, and Pharmacokinetics Group 4). Due to poor survival, all surviving high-dose (Group 3) animals were sacrificed during Week 80. In addition, surviving PK control animals (Group 4) were sacrificed at Week 80 to provide age-matched control tissues. The following listed tissues or representative samples were collected and preserved in 10% buffered formalin. Tissues designated with a single asterisk were weighed at the Week 53 scheduled sacrifice. Paired organs were weighed together. All masses and any lesions with possible histopathological correlates were retained. The identity of masses was maintained. Bone marrow smears were prepared and stained with Wright's stain from specimens collected from each animal sacrificed moribund and from all animals at scheduled necropsies. These smears were not examined.

| | | |
|---|---|---|
| Aorta | *Liver With Gallbladder Drained | Seminal Vesicle |
| *Adrenal Glands (Weighed Post Fixation) | *Lungs | Skin (Caudal, Abdominal Region) |
| Bone, Femur (Including Articular Surface) | Lymph Node, Submaxillary | Spinal Cord (Lumbar) |
| Bone, Sternum (Including Marrow) | Lymph Node, Mesenteric | *Spleen |
| Bone Marrow Smear (Except for Animals Found Dead) | Mammary Gland (Females Only, Attached To Skin) | *Stomach |
| *Brain | Nasal Turbinates | *Testes |
| *Cecum | *Ovaries | *Thymus |
| *Colon | Pancreas | Tongue |
| *Epididymides (Both) | *Pituitary Gland (Weighed Post Fixation) | Trachea |
| Esophagus | *Prostate | Urinary Bladder |
| Eyes With Harderian Gland | Salivary Gland, Submaxillary | *Uterus (With Cervix) |
| *Heart | Sciatic Nerve | Vagina |
| *Intestine, Small (Duodenum, Jejunum, Ileum) | Skeletal Muscle | Lesions And Masses |
| *Kidneys | *Thyroid Glands (with Parathyroid; Weighed Post Fixation)** | |
| **The parathyroid was weighed with the thyroid and was examined microscopically if it was included in the section of thyroid. | | |

- Histopathology - All tissues collected from the Toxicology animals (Groups N, 1, 2, and 3) and the Pharmacokinetics control animals (Group 4) that were sacrificed and necropsied at Week 80, were shipped to for processing and histopathologic examinations. Histological sections of all protocol-defined tissues and all lesions were prepared, stained with haematoxylin and eosin, and examined from all mice sacrificed by design during Weeks 53, 80, and 105-106, and from any Toxicology animal that died or was sacrificed moribund during the study. For each Toxicology animal that died or was sacrificed moribund, an apparent cause of moribundity or death was determined. This evaluation included whether a tumor or tumors contributed to the cause of death.

**Results:**

- Group Mean Dosages - Test article dosages were calculated using body weight data, food consumption data, and dose formulation information. Based on these calculations, the mean dosages for the study ranged as presented in the following table.

| Dose Group | Intended Dosage (mg/kg/day) | | Actual Dosage (mg/kg/day) | |
|---|---|---|---|---|
| | ♂ | ♀ | ♂ | ♀ |
| Low | 25<br>12.5 | 50<br>25 | | |
| Mid | 50<br>25 | 100<br>50 | | |
| High | 75<br>37.5 | 150<br>75[a] | | |

[a] Weeks 19 through 22

[b] During Weeks 2 and 3, calculated dosages were 70.65 and 70.39 mg/kg/day, respectively, for the mid-dose males; 63.03 and 70.73 mg/kg/day, respectively, for the low-dose females; and 56.38 and 54.52 mg/kg/day, respectively, for the mid-dose females.

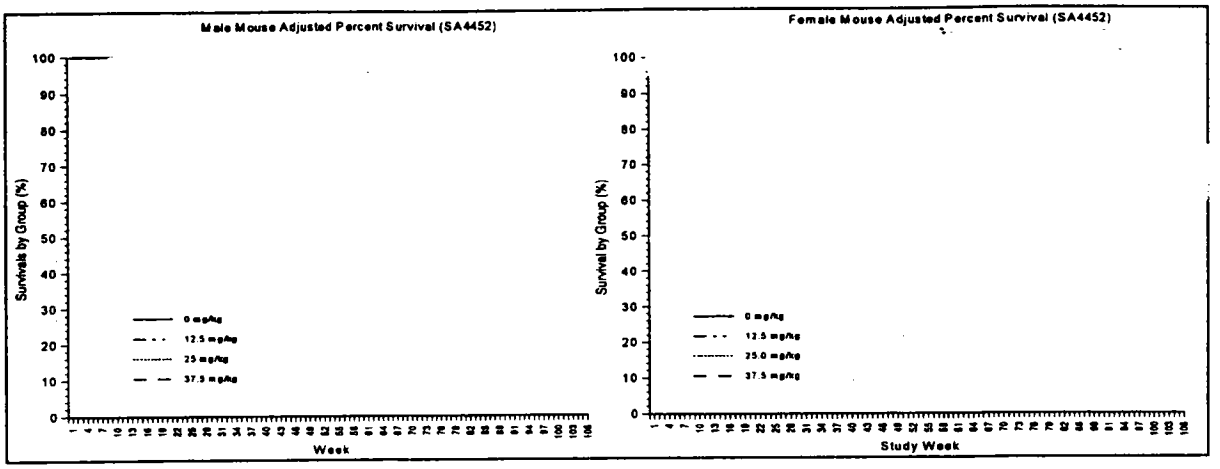


- Mortality and Clinical Signs - Test article related-deaths were noted in all SC-58635 treated groups. The incidences of treatment-related deaths increased as the dosage increased. Observations of urine-stained hair, intra-abdominal swelling, distended abdomen, piloerection, decreased defecation, and pale appearance were frequently noted for animals that died or were sacrificed in a moribund condition. Survival for ♂ and ♀ was statistically analyzed by life table methods using the National Cancer Institutes Package[4,5]. Adjusted survival was computed using

4 D. G. Thomas, N. Breslow, and J.J. Gart, 1977. Trend and homogeneity analyses of proportions and life table data, Comput. Biomed. Res., 10: 373-381.

5 J.J. Gart, D. Krewski, P.N. Lee, R.E. Tarone, and J. Wahrendorf, 1986. Statistical Methods in Cancer Research, Vol. III, The Design and Analysis of Long-Term Animal Experiments, Oxford University Press.

the Kaplan-Meier product limit estimation method and was plotted as proportion surviving versus time as illustrated in the following figures.




Two sets of analyses were performed for both sexes. In the first set, survival for Groups N through 3 were analyzed through Week 80 (termination of high dose group). In the second set, survival was analyzed for Groups N, 1 and 2 up to Week 106 (terminal sacrifice). Significantly reduced survivals were noted in low-, mid-, and high dose ♂, and high dose ♀. The survivals for each group are summarized in the following table. **Due to excessive toxicity, high dose group animals were sacrificed at Week 80.**

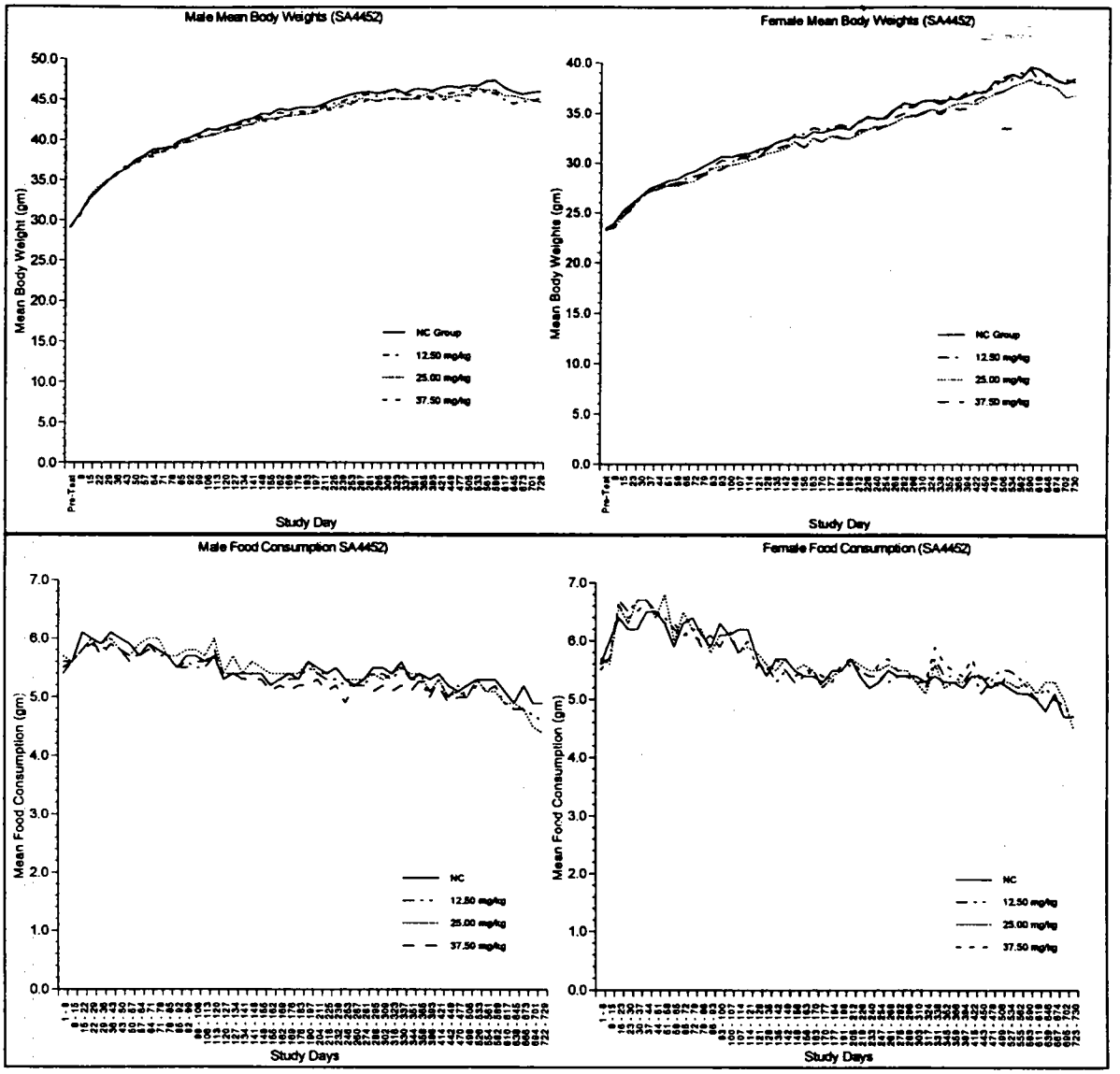
| Group | Dose (mg/kg) | | Week 80 | | | | Week 106 | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ♂ | ♀ | ♂ | | ♀ | | ♂ | | ♀ | |
| N | 0 | 0 | 68/79 | 86% | 61/79 | 77% | 39/73 | 53% | 26/73 | 36% |
| 1 | 12.5 | 25 | 63/80 | 79% | 61/79 | 77% | 26/78 | 33%** | 32/79 | 41% |
| 2 | 25 | 50 | 50/80 | 63% | 54/80 | 68% | 26/78 | 33%** | 25/78 | 32% |
| 3 | 75 | 150 | 29/80 | 36%** | 35/80 | 44%** | - | | - | |

* Statistically significant, $p<0.01$

- PK/TK - SC-58635 was orally absorbed and systemically available at all doses during the study. Exposure of SC-58635, as measured by $C_{max}$ and $AUC_{0-24}$, increased with dose and is shown in the following table. Male and female animals within each dose group were similarly exposed to test article on Day 3-4 of the study. However, on subsequent sampling days (Week 19, 52 and 78) plasma concentrations of SC-58635 were lower in female than in male mice when compared within each dose group for the low, mid and high doses.

| Week (Days) | Dose (mg/ kg) | | | | | $T_{max}$ (hr) | | $C_{max}$ ($\mu$g/ml) | | $AUC_{0-24}$ ($\mu$g•hr/ml) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Wk1-18 | Wk 19-104 | Wk1-18 | Wk19-22 | Wk 23-80 | | | | | | |
| | ♂ | | ♀ | | | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| 1 (3- 4) | 25 | 12.5 | 50 | 25 | 25 | 9 | 9 | 1.73 | 2.73 | 22.0 | 29.9 |
| | 50 | 25 | 100 | 50 | 50 | | | | | | |
| | 75 | 37.5 | 150 | 75 | 150 | | | | | | |
| 19 (126- 127) | 25 | 12.5 | 50 | 25 | 25 | 9 | 18 | 1.75 | 0. 815 | 32.8 | 14.3 |
| | 50 | 25 | 100 | 50 | 50 | | | | | | |
| | 75 | 37.5 | 150 | 75 | 150 | | | | | | |
| 52 (357- 358) | 25 | 12.5 | 50 | 25 | 25 | 9 | 9 | 0.723 | 0.558 | 13.2 | 8.14 |
| | 50 | 25 | 100 | 50 | 50 | | | | | | |
| | 75 | 37.5 | 150 | 75 | 150 | | | | | | |
| 78 (540- 541) | 25 | 12.5 | 50 | 25 | 25 | 9 | 9 | 0.933 | 0.813 | 16.4 | 12.9 |
| | 50 | 25 | 100 | 50 | 50 | | | | | | |
| | 75 | 37.5 | 150 | 75 | 150 | | | | | | |

- Body Weight and Food Consumption - There were no test article-related effects on body weight, cumulative body weight gain, and food consumption as depicted in the following figures.




Although a few statistically significant decreases in mean body weights for mid-and high-dose females during the first 13 weeks of the study and cumulative body weight gains for the high-dose ♂ and the low-, mid- and high-dose ♀ during 1st week of study, for the mid-dose ♀ at Week 10, and for the high-dose ♀ at Weeks 2 and 3 and Weeks 9 to 13 were observed, these changes were not considered toxicologically significant as the differences were transient, sporadic. There were occasional statistically significant differences (↑ or ↓) in food consumption for all treated groups compared to the control group. All changes seen were within published ranges[6] and were not considered biologically significant.

- Clinical Chemistry - No treatment-related changes in clinical chemistry parameters were observed. Although statistically significant differences were observed in a few parameters, these

6 Andress, J.M, 1992. The Mouse; Toxicology. In: Animal Models in Toxicology, eds., Gad S.C., Chengelis, C.P. New York: Marcel Dekker, Inc., p. 165-232.

changes were either of low magnitude or non-dose dependent and might not have any biological impact. The changes seen were as followings:

| Changes | Chemistry Parameter | Group | Week | Observation |
|---|---|---|---|---|
| ↑ | Ca | mid- and high-dose ♀ | 53 | ↑ 5% |
| | Globulin | high-dose ♂ | 80 | ↑ 22% |
| | Triglycerides | low-dose ♀ | 105-106 | ↑ 49% |
| | Total Protein | mid-dose ♀ | 105-106 | ↑ 11.5% |
| | K | mid-dose ♀ | 105-106 | ↑ 18% |
| ↓ | Total Bilirubin | high-dose ♀ | 80 | ↓ 36% |
| | Glucose | high-dose ♀ | 80 | ↓ 26% |
| | Albumin | high-dose ♂ & ♀ | 80 | ↓ 10 and 16%, respectively |
| | Bile Acids | mid-dose ♀ | 105-106 | ↓ 37% |

Several individual animals in all dose groups (including control) at scheduled or moribund sacrifices showed slight to marked alterations in a few clinical chemistry parameters. These changes usually correlated with the presence of spontaneous, age-related lesions and/or moribundity as evidenced by gross and/or histopathologic evaluations.

- Necropsy Findings -

Unscheduled Deaths (found dead, moribund sacrifice, unscheduled sacrifice): Treatment-caused macroscopic lesions were observed in the GI tract (glandular stomach, small and large intestine). These lesions were characterized as erosion/ulceration and/or perforation of one or more segments of gastrointestinal tract, abdominal visceral adhesions, and abnormal peritoneal contents (due to leakage of gastrointestinal contents into the peritoneal cavity). The following table summarizes the incidence of macroscopic gastrointestinal lesions (erosion/ulceration, perforation and associated changes) in mice that died or were sacrificed in a moribund condition.

| Group | N | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|
| ♂ | 1/35 | 3/52 | 14/52 | 27/51 | 0/1 | 0/13 | 7/13 | 3/9 |
| ♀ | 1/48 | 3/48 | 8/53 | 33/45 | 0/3 | 0/11 | 3/11 | 7/14 |
| Total | 2/83 | 6/100 | 22/105 | 60/96 | 0/4 | 0/24 | 10/24 | 10/23 |

Histologic examinations were performed on Toxicology animals only (Groups N, 1, 2, and 3). Microscopic changes observed in GI included ulceration, erosion, and necrosis of GI mucosa and chronic active inflammation of serosal surfaces (peritonitis) of the abdominal viscera. Morphologic changes as described above were also identified in two control animals; these were considered to be spontaneously occurring age-related lesions occasionally seen in the gastrointestinal tract of aging laboratory mice.

Scheduled Sacrifices:

**Week 53 Interim Sacrifice** (Groups N, 1, 2, and 3): Treatment-related macroscopic findings included small intestinal (jejunum or ileum) adhesions or mass/nodule in 4 animals (1 Group 1 ♂, 1 Group 3 ♂, 1 Group 2 ♀, and 1 Group 3 ♀). These lesions have microscopic characteristics of chronic active inflammation of the mucosa and/or serosa (peritonitis). The jejunal mass/nodule in another high-dose male was Peyer's patch hyperplasia. All other gross findings were commonly seen in CD-1 mice of this age and occurred with similar incidence among control and SC-58635-treated groups.

**Week 80 Terminal Sacrifice** (Groups 3 and 4): Treatment-related toxicological findings at Week 80 were gastrointestinal (stomach, jejunum) adhesions and/or ulceration/erosion in the high-dose group (3 ♂ and 6 ♀) with microscopic characteristics of mucosal erosion/ulceration and/or chronic active inflammation of the serosa (peritonitis). All other gross findings were commonly seen in CD-1 mice of this age and occurred with similar incidence among control and SC-58635-treated groups.

**Weeks 105-106 Terminal Sacrifice** (Groups N, 1, and 2): At terminal necropsy, treatment-related GI changes (gastrointestinal adhesions and/or ulceration/erosion) with microscopic characteristics of mucosal erosion/ulceration and/or chronic active inflammation of the serosa (peritonitis) were seen in Group 2 animals (5♂ & 1♀). All other findings at were commonly seen in CD-1 mice of this age and occurred with similar incidence between control and SC-58635-treated groups.

- Histopathology -

Non-neoplastic Lesions: Treatment-caused histpathological changes were limited to the GI tract. The following table summarizes the incidence of erosion/ulceration in one or more segments of gastrointestinal tract at various sacrifice intervals.

| Sacrifice Intervals | | N | | 1 | | 2 | | 3 | |
|---|---|---|---|---|---|---|---|---|---|
| | | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| Wk 53 | Nº Examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | Incidence | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1 |
| Wk 80 | Nº. Examined | 0 | 0 | 0 | 0 | 0 | 0 | 29 | 35 |
| | Incidence | - | - | - | - | - | - | 2 | 5 |
| Wk 105/106 | Nº. Examined | 45 | 32 | 32 | 38 | 32 | 31 | - | - |
| | Incidence | 0 | 1 | 1 | 1 | 2 | 1 | - | - |
| Unscheduled | Nº. Examined | 35 | 48 | 52 | 47 | 52 | 53 | 51 | 45 |
| Deaths | Incidence | 1 | 1 | 3 | 3 | 6 | 6 | 19 | 20 |
| Total Incidence | | 1 | 2 | 4 | 4 | 9 | 7 | 22 | 26 |

Gastrointestinal tract sites include glandular stomach, duodenum, jejunum, ileum, cecum, and colon. Glandular stomach lesions of animals in this table were all perforating ulcers (Grade 5).

Treatment-related GI lesions (erosion/ulceration with associated chronic active inflammation) were observed in the glandular stomach, duodenum, jejunum, ileum, cecum, and colon at one or more sites, mainly present in the glandular stomach, jejunum and ileum. The severity and distribution of these GI lesions were dose-dependent. GI injury noted in animals that died or were sacrificed at moribund was more severe than those seen at scheduled sacrifice. Chronic active inflammation of the serosal surfaces (peritonitis) of several abdominal organs secondary to the GI injury was also noted. The most common involved tissues in serosal inflammation were: GI tract, adrenals, pancreas, kidney, gall bladder, ovary, uterus, seminal vesicles, urinary bladder, mesenteric lymph nodes, and liver.

Occasionally, microscopic GI lesions were observed in a few animals with no gross morphologic alterations and vice versa. The following table presents the combined total incidence (gross and/or microscopic) of treatment-induced gastrointestinal lesions. Glandular stomach lesions included in this table were perforating ulcers (Grade 5 lesions) only.

| | Group | | |
|---|---|---|---|
| | 1 (Low-Dose) | 2 (Mid-Dose) | 3 (High-Dose) |
| ♂ | 5 | 21 | 32 |
| ♀ | 4 | 10 | 40 |



The gastrointestinal lesions with or without associated chronic active inflammation of serosal surfaces (peritonitis) of abdominal viscera (as described in SC-58635-treated animals) were also observed in some control animals. These were considered spontaneous lesions occasionally seen in the gastrointestinal tract of aging laboratory mice.

The GI injury was the most common cause of death in high-dose animals. Some animals in the mid- and low-dose groups also died of test article-related GI injury. Other common causes of death as evaluated by macro- and microscopic examinations were: amyloid deposition, lymphoma, and mouse urologic syndrome (a common spontaneous finding in male mice). The incidence of common causes of death, other than treatment-related GI injury, was similar in all

groups or was within the historical data published for CD-1 mice[7,8]. **Amyloidosis occurs frequently in aged CD-1 mice and is the major cause of death. It appears to begin as a deposition of amyloid in the submucosa of the duodenum, jejunum, and ileum. In severe cases, many other organ are also involved; involvement of the glomeruli of kidneys is usually the cause of death in animals that die with amyloidosis**[9].

The following table lists the most common causes of death in male and female mice as evidenced by pathologic evaluations.

| Pathological Findings | N | | 1 | | 2 | | 3 | |
|---|---|---|---|---|---|---|---|---|
| | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| Gastrointestinal Lesions[a] | 0 | 1 | 2 | 2 | 8 | 5 | 24 | 30 |
| Amyloid Deposition | 5 | 5 | 5 | 0 | 4 | 4 | 3 | 1 |
| Lymphoma | 8 | 7 | 4 | 7 | 4 | 8 | 2 | 2 |
| Mouse Urologic Syndrome | 6 | - | 17 | - | 9 | - | 7 | - |
| Multiple Causes[b] | 8 | 7 | 15 | 12 | 19 | 7 | 6 | 3 |



[a] Includes animals with erosion/ulceration of the glandular stomach or intestine chronic inflammation of the serosa surfaces (peritonitis) of various abdominal tissues

[b] Multiple causes (include any combination of GI lesions, amyloid deposition, inflammatory lesions in skin, urinary tract, other tissues, and/or lymphoma, and various other neoplasms).

Other common lesions observed in SC-58635-treated male and/or female mice with slightly higher incidence compared with control included: increased hematopoiesis in the spleen, myeloid hyperplasia in the sternal and femoral bone marrow, hematopoiesis in the liver, and leukocytosis in the liver and lung. These findings occurred mainly in animals with gastrointestinal injury and/or prominent neoplastic or inflammatory lesions in various tissues. These findings were considered secondary changes in response to inflammation and/or tissue damage. A decreased incidence of several non-neoplastic (e.g., amyloidosis and mineralization in brain, eye, and testis) lesions was also observed in the high-dose groups (♂: 37.5 mg/kg/day; ♀: 150 mg/kg/day). This decrease was attributable to the shorter lifespans in these groups as high test article-related motality observed and earlier group termination (Week 80). The incidence of test article-related gastrointestinal lesions was statistically significant for ♂ & ♀ in the mid-and high-dose groups. In addition, the incidence of chronic active inflammation of serosal surfaces of abdominal organs, secondary hematopoietic changes in bone marrow, spleen, liver, and lung, and decreased incidence of several spontaneous neoplastic and non-neoplastic lesions were statistically significant in one or more treatment groups. Low and statistically non-significant incidence of pyelonephritis was observed in SC-58635 treated ♂ mice (0/97, 6/94, 2/94, 3/90 for Groups N, 1-3, respectively) that died or sacrificed at moribund. **Although this observation was not dose-related and occured at very low incidence, treatment-attributable nephrotoxicity could not be ruled out as nephropathy was observed in mice treated with this compound at 1000 mg/kg for 2 weeks. In addition, pyelonephritis was commonly seen in animals treated with NSAIDs.**

The incidence of major non-neoplastic findings (statistically significant at 5 or 1%) for each group, including data from the Satellite animals, during entire period of study are summarized in the following table.



7 Maita, K., Hirano, M., Harada, T., Mitsumori, K., Yoshida, A., Takahashi, K., Nadashima, N., Kitazawa, T., Enomoto, A., Inui, K., Shirasu, Y,1988. Mortality, major cause of moribundity, and spontaneous tumors in CD-1 mice, Toxicol Pathol, 16(3): 340-349.

8 Chandra, M. and C.H. Frith, 1992. Spontaneous neoplasms in aged CD-1 mice, Toxicol Letters, 61: 67-74.

9 Frith, C.H., Goodman, D.G., and Boysen, B.G., 1992. The Mouse; Pathology. In: Animal Models in Toxicology, eds., Gad S.C., Chengelis, C.P. New York: Marcel Dekker, Inc., p. 165-232.

| Non-neoplastic Findings | Incidence Rates | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Group N | | Group 1 | | Group 2 | | Group 3 | |
| | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| Adrenal - Serosa, Inflammation, Chronic Active | 1/97 | 1/95 | 1/94 | 3/95 | 3/94 | 1/94 | 13/90** | 14/90** |
| Bone Marrow, Femur - Hyperplasia, Myeloid | 19/97 | 24/95 | 29/94 | 34/95 | 38/94** | 26/94 | 27/90* | 43/90** |
| Bone Marrow, Sternum - Hyperplasia, Myeloid | 28/97 | 26/95 | 39/94* | 34/94 | 48/94** | 31/94 | 35/90* | 43/90** |
| Brain - Cerebrum, Infiltrate, Lymphocytic, Perivascular | 0/97 | | 0/94 | | 2/94 | | 2/90 | |
| Epididymis - Serosa, Inflammation, Chronic Active | 1/97 | | 1/94 | | 1/93 | | 3/90 | |
| Gallbladder - Serosa, Inflammation, Chronic Active | 0/96 | 0/91 | 1/92 | 1/94 | 1/90 | 1/93 | 4/89* | 8/87** |
| Intestine-large, Cecum - Serosa, Inflammation, Chronic Active | 0/97 | 0/95 | 1/94 | 1/94 | 0/94 | 2/94 | 3/90 | 11/90** |
| Intestine-large, Colon - Serosa, Inflammation, Chronic Active | 0/97 | 0/94 | 2/94 | 0/93 | 0/94 | 1/94 | 3/90 | 9/90** |
| Intestine-small, Duodenum - Erosion/Ulceration | | 0/95 | | 1/94 | | 1/94 | | 2/90 |
| Intestine-small, Duodenum - Serosa, Inflammation, Chronic Active | 0/97 | 0/95 | 0/94 | 0/94 | 5/94 | 3/94* | 1/90 | 6/90** |
| Intestine-small, Ileum - Erosion/ulceration | 0/97 | 0/95 | 1/94 | 2/95 | 5/94** | 5/94** | 6/90** | 9/90** |
| Intestine-small, Ileum - Serosa, Inflammation, Chronic Active | 3/97 | 0/95 | 1/94 | 3/95 | 8/94* | 7/94 | 13/90** | 20/90** |
| Intestine-small, Jejunum - Erosion/ulceration | 1/97 | 2/95 | 1/94 | 1/95 | 5/94* | 0/94 | 6/90** | 9/90** |
| Intestine-small, Jejunum - Serosa, Inflammation, Chronic Active | 1/97 | 2/95 | 2/94 | 1/95 | 11/94** | 4/94 | 11/90** | 20/90** |
| Kidney - Pyelonephritis | 0/97 | | 6/94 | | 2/94 | | 3/90 | |
| Kidney - Serosa, Inflammation, Chronic Active | 1/97 | 0/95 | 1/94 | 1/95 | 3/94 | 3/94 | 7/90** | 7/90** |
| Liver - Hematopoiesis | 4/97 | 13/95 | 21/94 | 16/95 | 15/94** | 18/94 | 28/90** | 33/90** |
| Liver - Hepatocellular Hypertrophy, Centrilobular | 1/97 | | 3/94 | | 3/94 | | 3/90 | |
| Liver - Hepatocellular Necrosis | 6/97 | | 5/94 | | 6/94 | | 9/90 | |
| Liver - Leukocytosis | 2/97 | 6/95 | 2/94 | 5/95 | 3/94 | 7/94 | 9/90** | 20/90** |
| Liver - Serosa, Inflammation, Chronic Active | 1/97 | 0/95 | 0/94 | 2/95 | 4/94 | 3/94 | 9/90** | 16/90** |
| Lung - Leukocytosis | 1/97 | 7/95 | 1/93 | 7/95 | 3/94 | 8/94 | 10/90** | 17/90** |
| Lymph Node, Mesenteric - Hyperplasia, Lymphoid | 3/95 | 1/91 | 6/91 | 3/94 | 8/90 | 5/91* | 9/82** | 5/86* |
| Lymph Node, Mesenteric - Inflammation, Chronic Active | 6/95 | 3/91 | 7/91 | 3/94 | 6/90 | 3/91 | 8/82 | 6/86 |
| Lymph Node, Mesenteric - Serosa, Inflammation, Chronic Active | 3/95 | 0/91 | 0/91 | 2/94 | 2/90 | 3/91 | 6/82* | 15/86** |
| Mammary Gland - Inflammation, Chronic Active | | 0/94 | | 0/95 | | 0/91 | | 4/89* |
| Nasal Turbinate - Respiratory Mucosa, Cyst | 0/96 | | 0/92 | | 0/91 | | 4/83** | |
| Ovary- Serosa, Inflammation, Chronic Active | | 2/94 | | 2/95 | | 3/93 | | 15/90** |
| Pancreas - Serosa, Inflammation, Chronic Active | 2/97 | 2/95 | 2/94 | 2/95 | 9/94** | 5/94 | 17/90** | 24/90** |
| Seminal Vesicle - Serosa, Inflammation, Chronic Active | 0/97 | | 3/94 | | 1/94 | | 10/90** | |
| Spleen - Hematopoiesis, Increased | 21/97 | 52/95 | 36/93* | 55/94 | 48/92** | 46/93 | 39/90** | 66/90* |
| Spleen - Serosa, Inflammation, Chronic Active | 1/97 | | 2/93 | | 0/92 | | 5/90* | |
| Stomach - Glandular, Erosion/Ulceration | | 5/95 | | 5/95 | | 9/94 | | 26/90** |
| Stomach - Glandular, Inflammation, Chronic Active | | 0/95 | | 0/95 | | 3/94* | | 2/90* |
| Stomach - Serosa, Inflammation, Chronic Active | 2/97 | 1/95 | 3/94 | 3/95 | 6/94 | 6/94* | 23/90** | 34/90** |
| Urinary Bladder - Concretion | 0/97 | | 0/94 | | 0/94 | | 3/90* | |
| Urinary Bladder - Serosa, Inflammation, Chronic Active | 1/97 | 0/94 | 0/94 | 0/95 | 0/94 | 1/93 | 6/90** | 11/90** |
| Uterus - Serosa, Inflammation, Chronic Active | | 0/95 | | 0/95 | | 3/94* | | 7/90** |

*p<0.05; **p<0.01

Neoplastic Lesions: Treatment of SC-58635 did not increase the incidence of all examined tumors. The incidence of spontaneous common neoplasms was similar and statistically non-significant between control and SC-58635 treated groups. An apparent positive trend in the incidence of pars distalis adenoma of the pituitary in the females (p=0.0192) was observed. It is not statistically significant as pituitary adenoma is a common tumor in female CD-1 mice ( with a mean of approximately 4%). All other neoplastic lesions did not exhibit a clear dose-related increase in incidence or severity. The following table shows major neoplastic findings (incidence rates) for each group.

| Neoplastic Findings | Group N | | Group 1 | | Group 2 | | Group 3 | |
|---|---|---|---|---|---|---|---|---|
| | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| Adrenal Gland: Subcapsular Cell Adenoma (I) | 3/97 | 0/95 | 2/94 | 1/95 | 6/94 | 0/94 | 0/90 | 1/90 |
| All Tissues: Lymphoma (I+F) | 11/97 | 14/95 | 11/94 | 17/95 | 8/94 | 13/95 | 3/90 | 3/90 |
| All Tissues: Hemagioma | 0/97 | 3/95 | 3/94 | 1/95 | 1/94 | 3/94 | 0/90 | 0/90 |
| All Tissues: Hemagiosarcoma | 4/97 | 5/95 | 3/94 | 3/95 | 10/94 | 4/94 | 2/90 | 1/90 |
| Lung: Bronchiolar/Alveolar Adenoma/Carcinoma (I+F) | 32/97 | 18/95 | 32/93 | 26/95 | 29/94 | 19/94 | 10/90 | 3/90 |
| Pituitary, Pars Distalis Adenoma (I+F) | 1/94 | 2/92 | 0/94 | 4/93 | 1/92 | 5/89 | 1/90 | 2/88* |

I = Incidental; F = Fatal.

Therefore, dietary administration of SC-58635 to mice for ≥104 weeks caused gastrointestinal toxicity and mortality in all dose groups and it is not carcinogenic as similar incidence of examined tumors was noted in all groups. Non-dose dependent pyelonephritis was only observed in drug-treated ♂ with low incidence rates. The dosages used in this carcinogenicity assessment study exceeded a Maximum Tolerated Dose (MTD) in all treatment groups and the NOAEL for either ♂ or ♀ could not be determined.

## 2.4. REPRODUCTIVE TOXICOLOGY

### *2.4.1. FERTILITY STUDIES*

2.4.1.1. Study Of Fertility And Early Embryonic Development To Implantation With SC-58635 By Oral Administration In The Rat, Document No.: PSA95C-30-SA4294; Date: 15-May-1995 (Vol. 1.55, p. 1-339 & Vol. 1.56, 1-230)

Included as an appendix to this report was:
Evaluation Of The SC-58635 Plasma Concentration Data From The Study Of Fertility And Early Embryonic Development To Implantation With SC-58635 By Oral Administration In The Rat, SA4294, Document No.: MRC-95S-0086; Date: 27-Apr-1995 (Vol. 1.56, p. 179-193)

Study Nº: SA4294/B 95723
Report Nº: PSA95C-30-SA4294
Study Aim: To evaluate the effects of SC-58635 on fertility and early embryonic development in Sprague-Dawley rats
Compound: SC-58553 (Lot Nº 94K014-A1B, -A3B) suspension in 0.5% methylcellulose (w/v) & 0.1% polysorbate 80 (v/v) in $H_2O$

Dose & Route:
♂: 0, 60, 300, and 600 mg/kg/day po, at least 28 days prior to mating, throughout the study.
♀: 0, 60, 300, and 600 mg/kg/day po, 14 days prior to placement for mating, during the mating period and in gestation from Day 0 to 7.

Control Vehicle: 0.5% methylcellulose (w/v) & 0.1% polysorbate 80 (v/v) in $H_2O$
Animals: 115♂ & 115♀ Sprague-Dawley rats, strain Crl:CD®(SD)BR; Age: 12 & 10 wk old for ♂ and ♀, respectively; weighing g for ♂ and g for ♀ rats.
Study Location:

Study Date: 10/4/1994 - 1/23/1995
Compliance with GLP/QAU: Yes
Study Design:

| Group | Dose (mg/kg/day) | Nº of Rats | | |
|---|---|---|---|---|
| | | Treated | | Untreated |
| | | ♂ | ♀ | ♀ |
| Vehicle Control | 0 | 25 | 25 | 25 |
| SC-58635 | 60 | 25 | 25 | 24* |
| SC-58635 | 300 | 25 | 25 | 25 |
| SC-58635 | 600 | 25 | 25 | 25 |

*Assigned male died prior to mating with untreated females.

The following parameters were investigated: clinical signs; body weight (measured on Gestation Days 0, 3, 7, 10 and 13); food consumption recorded for the mated females (treated and untreated) during gestation intervals 0-3, 3-7, 7-10 and 10-13; estrous cycles; uterine examination on Gestation Day 13; PK; and terminal gross pathological examinations; sperm mortality; spermatozoa counts and morphology of spermatozoa.

**Results:** One ♂ in both the control and the 60 mg/kg/day groups died of unknown causes during the study. One ♂ in 600 mg/kg/day was killed on Day 102 in a moribund condition as a result of esophageal perforation. No treatment related clinical findings were noted for the male or treated females. There was no effects on body weights. Food consumption was increased for males receiving 300 mg/kg/day from weeks 2 to 3 and for females from weeks 1 to 2 of the premating

period. No gross pathological findings were treatment related. The estrous cycles of the SC-58635 treated females were not affected. The mating and fertility indices, conception rates and mean day of mating were unaffected in all animals. Sperm motility, spermatozoa counts and morphology were not changed by the treatment. The number of live fetuses and implantation sites were significantly lower in all SC-58635 treated groups. Significantly higher preimplantation losses were seen for the all treated females and this SC-58635 induced preimplantation loss was dose-dependent.
In conclusion, male fertility was not affected by SC-58635 treatment at the dose levels up to 600 mg/kg/day. For the treated females, the number of live fetuses was significantly lower and significantly higher preimplantation losses at dose levels ≥60 mg/kg/day.

2.4.1.2. Study Of Fertility And Early Embryonic Development To Implantation With SC-58635 By Oral Administration In The Female Rat, (SA 4345), Document No.: P30S4345; Date: 04-Nov-1996 (Vol. 1.57, 1-272)

Study Nº: SA4345/95813
Report Nº: P30S4345
Study Aims: To investigate the effects of SC-58635 on fertility and early embryonic development in female rats after oral administration.
Compound: SC-58635 (Lot Nº: 94K014-A3B, 99.8% purity)
Vehicle: 0.5% Methylcellulose

| Group | Dose (mg/kg/day) | Nº of ♀ |
|---|---|---|
| 1 (Vehicle Control) | 0 | 25 |
| 2 | 15 | 25 |
| 3 | 30 | 25 |
| 4 | 50 | 25 |
| 5 | 300 | 25 |



Dose and Route: 15, 30, 50, and 300 mg/10 ml/kg/day po by gavage
Animals: 125♀ Sprague-Dawley rats, Crl:CD®(SD)BR, 10 weeks of age, weighing 25/group.
Study Date: 2/7/95 (1st day of treatment) - 3/26/95 (necropsy)
Study Site:

GLP/AUC: Yes
Study Design: The female rats were given SC-58635 or vehicle control daily from 14 days prior to mating, throughout the mating and through Gestation Day 7. The following observations were conducted:

- Clinical Signs and Mortality - 2x/day.
- Body Weight and - 1x/week during premating treatment period and Gestation Days 0, 3, 7, 10, and 13.
- Food consumption - 1x/week during premating treatment period and Gestation Days 0-3, 3-7, 7-10, and 10-13.
- Necropsy - on Gestation Day 13. The reproductive tract was removed and the corpora lutea were counted. The uterine contents were examined. The following tissues were preserved: uterus, mammary glands (cervical and inguinal), vagina, ovaries, and any abnormalities.
- Mating and fertility indices, and the conception rates were calculated as follows:
  Mating Index (%) = (Nº of females mating)/(Nº of females placed for mating) x 100
  Fertility Index (%) = (Nº of females pregnant)/(Nº of females placed for mating) x 100
  Conception Rate (%) = (Nº of pregnant females)/(Nº of mated females) x 100
- Reproductive Indices were calculated as follows:
  Preimplantation loss (%) = (Nº of corpora lutea - Nº of implants)/(Nº of corpora lutea) x 100

Post implantation loss (%) = (Nº of implants - Nº of live embryos)/(Nº of implants) x 100

**Results:**

- Mortality and Clinical Findings- One ♀ @ 50 mg/kg/day died on study Day 29 prior to mating due to the handling error with macroscopic findings of pulmonary edema and fluid in the tracheal lumen and a clot in the cranial cavity. Because mating was not observed, a ♀ @ 50 mg/kg/day was sacrificed at the end of the mating period and was found to be pregnant. No remarkable clinical signs were noted attributable to the treatment.
- Body Weight and Food Consumption - No treatment related effects were observed. Food consumption values for the 15 mg/kg/day treated females were significantly lower during the prestudy period.
- Gross Pathological Findings - Adhesion between the liver and adjacent structures, such as the diaphragm or intra-abdominal fat was seen in 3 females @ 300 mg/kg/day. This change was associated with intrahepatic abnormalities, such as depressed and/or dark and/or pale area(s). The sponsor stated that these findings were incidental. Dark mucoid material in the vaginal lumen was the most frequent observation in all groups.
- Estrous Cycles - Not affected.
- Reproductive Performance and Parameters - The mating and fertility indices, conception rates and mean day of mating were unaffected. The numbers of corpora lutea were significantly ↓ for the 300 mg/kg/day group. Significantly decreased numbers of implantation sites and live embryos were seen in the females @ 50 and 300 mg/kg/day. These reductions resulted in significantly ↑ pre- and post implantation losses (%) in these groups. The following table shows reproductive indices for each group.

| Reproductive Indices | Dose (mg/kg/day) | | | | |
|---|---|---|---|---|---|
| | Vehicle Control | 15 | 30 | 50 | 300 |
| Nº of Corpora Lutea | 17.5±2.04 | 17.3±3.15 | 17.6±2.33 | 17.2±2.80 | 15.7±2.42** |
| Nº of Implantation Sites | 16.5±1.90 | 16.3±2.65 | 16.9±2.09 | 14.0±3.76* | 11.4±4.56*** |
| Nº of Live Embryos | 15.4±1.74 | 14.4±3.33 | 14.9±2.61 | 11.6±4.41*** | 9.4±4.18*** |
| Nº of Dead Embryo | 0.0±0.21 | 0.0±0.00 | 0.0±0.00 | 0.1±0.23 | 0.0±0.00 |
| Nº of Early Resorption | 1.0±1.17 | 1.9±1.94 | 2.0±1.61 | 2.4±3.55 | 2.0±1.93 |
| % Preimplantation Loss | 5.8±6.52 | 5.7±7.37 | 4.0±5.12 | 18.0±19.21* | 27.7±25.40*** |
| % Post Implantation Loss | 6.4±6.67 | 11.9±12.81 | 12.0±9.34 | 16.7±21.02* | 20.3±21.90** |

Significantly different from control value: *p<0.05; **p<0.01; ***p<0.001 (Mann-Whitney).

In conclusion, no evidence of SC-58635 induced toxicity was observed in the females at any dose level. There was no affect on mating and fertility indices, conception rates or the mean day of mating when female rats were treated with SC-58635 at dose levels up to 300 mg/kg/day. For the treated females, the numbers of implantation sites and live embryos were significantly ↓ at dose levels of ≥50 mg/kg/day that resulted in significantly ↑ pre- and post-implantation losses. In addition, significant reductions in the numbers of corpora lutea were seen in the ♀ @ 300 mg/kg/day. Therefore, the NOAEL was 30 mg/kg/day for female rats in this study.

2.4.1.3. Study Of Fertility And Early Embryonic Development Through Implantation With SC-58635 In The Female Rat (2 Week Oral Administration Followed By 2 Week Reversal Prior To Mating)(SA 4402), Document No.: P30S4402; Date: 26-Aug-1996 (Vol. 1.57, p. 273-464)

| | |
|---|---|
| Report Nº: | P30S4402 |
| Study Nº: | SA4402 |
| Study Aim: | To evaluate the reversibility of SC-58635 induced effect on fertility and early embryonic development in female rats |
| Compound: | SC-58635 (Lot Nº 94K014-A3B) |

Vehicle Control: 0.5% (w/v) methylcellulose and 0.1% Polysorbate in distilled and deionized $H_2O$

Dose & Route: 0, 60 and 300 mg/kg/day po by gavage

Animals: 75 ♀ Sprague-Dawley rats, Crl:CD®(SD)BR, weighing 177-245 g, 8-9 weeks of age, 25/group

| Group | Dose (mg/kg/day) | Nº of ♀ |
|---|---|---|
| 1 | 0 | 25 |
| 2 | 60 | 25 |
| 3 | 300 | 25 |

Study Location:

Compliance with GLP/QAU: Yes

Study Date: 6/13/95 - 8/6/95

Study Design: The animals were orally dosed with SC-58635 daily for 14 days followed by a 14-day reversal period before mating. The following parameters were monitored.

- Mortality and Clinical Signs - 2x/day.
- Physical Examination - 1x/week.
- Body Weight & Food Consumption - Gestation Days 0, 3, 7, 10, and 13.
- Necropsy - Gestation Day 13.
- Estrous Cycles - The estrous cycles were determined for 10 days prior to mating.
- Mortality and Clinical Signs - No death occurred. No treatment-related clinical signs were noted.
- Body Weight & Food Consumption - No SC-58635 treatment related effects were noted.
- Estrous Cycles - The estrous cycles were not altered.
- Maternal Reproductive Performance - Neither mating nor fertility indices were affected. Conception rates in the treated ♀ were comparable to the control. There were no significant changes in the numbers of corpora lutea, implantation sites, live and dead fetuses, early absorption or pre and post implantation losses.
- Necropsy - No remarkable findings were obtained during gross pathological examination.

**Results:** In the previous study (Study Nº SA4294)(2.3.1.1.), results showed that SC-58635 at doses ≥60 mg/kg caused a significant ↓ in the numbers of live fetuses and ↑ in the preimplantation losses when ♀ rats were treated with SC-58635 14 days before mating, and through Gestation Day 7. These effects were not observed in the present study when treated females were allowed to have a 14-day recovering period before mating. The length of treatment with SC-58635 in the current study was shorter than that indicated in the Study Nº SA4294. Therefore, under the current study condition, the effects of SC-58635 on female reproductive performance might be reversible.

*2.4.2. TERATOLOGY STUDIES*

2.4.2.1. An Embryo-Fetal Developmental Toxicity Study Of SC-58635 In Rats, SA 4362, Document No.: PSA95S-30-SA4362; Date: 06-Dec-1995 (Vol. 1.58, p. 1-172)

Included as an appendix to this report was:
Evaluation Of Plasma SC-58635 Concentrations In An Embryo-Fetal Developmental Toxicity Study In Rats, SA 4362, Document No.: MRC95S-30-950168; Date: 22-Sep-1995 (Vol. 1.58, p. 146-168)

Study Nº: SA4632

Report Nº: PSA95S-30-SA4632

Study Aim: To determine the possible adverse effects on the pregnant female rats and on the development of the embryo and fetus following multiple oral administration of SC-58635 on Gestation Days 7-18.

Compound: SC-58635 (Lot Nº 94K014-A3B) suspension in 0.5% methylcellulose (w/v), 0.1% polysorbate 80 (v/v) in dist. $H_2O$

Dosage & Route: 0, 10, 30, and 100 mg/kg/day, 10 ml/kg po from Gestation Days 6-17 for 12 days

Animals: ♀ Charles River (VAF) CD strain rats, weighing g, ~4 months of age, 20/group for the Study Nº SA4632, and 6/group and 2 in the control group for the companion PK study

Study Location: G.D. Searle, Skokie, IL

Compliance with QAU: Yes

Study Design: Pregnant female rats were dosed with SC-58635 at 0, 10, 30, or 100 mg/kg/day for 12 days (Gestation Days 6-17). All animals were observed for clinical signs at least once daily. All animals were sacrificed on Gestation Day 20. All maternal and fetal data were collected at necropsy. Blood samples were collected on Gestation Days 6 & 16 at 2, 3, 4, and 24 hr post dosing. Plasma SC-58635 concentrations were determined by a

**Results:**

- Clinical Observations & Mortality - One at 100 mg/kg in the companion PK study died due to dosing error. Two animals in the control group were excluded from the study due to inadvertent deprivation of $H_2O$ intakes. No remarkable treatment-related clinical signs were noted.
- Food Consumption and Body Weight - No treatment-related changes were seen.
- Maternal Reproductive Performance - The data from any reproductive indices (Nº of corpora lutea, implantations, resorptions, dead fetuses, preimplantation loss, and postimplantation loss) were comparable across all dose groups. There was a slight but not statistical significant decrease in the of live fetuses observed in the 100 mg/kg group. The mean (±SD) live fetuses for control, 10, 30, and 100 mg/kg Groups were 13.7±2.1, 13.8±2.0, 13.5±2.0, and 12.1 ±3.0, respectively.
- Toxicokinetics - Dose-dependent but not dose-proportional increases in $C_{max}$ and AUC were noted on Gestation Days 6 & 16. The summarized PK parameters obtained on Gestation Days 6 & 16 are presented in the following table. $C_{max}$ and AUC values were higher on Gestation Day 16 than those values obtained on Gestation Day 6 for the animals receiving 10 and 30 mg/kg/day indicating that accumulation of SC-58635 had occurred after repeated dosing.

| Parameter | 10 mg/kg | | 30 mg/kg | | 100 mg/kg | |
|---|---|---|---|---|---|---|
| | Gestation Day 6 | Gestation Day 16 | Gestation Day 6 | Gestation Day 16 | Gestation Day 6 | Gestation Day 16 |
| $AUC_{0\text{-}24}$ ($\mu$g•hr/ml) | | | | | | |
| AUC/Dose | | | | | | |
| $C_{max}$ ($\mu$g/ml) | | | | | | |
| $C_{max}$/Dose | | | | | | |
| $T_{max}$ (hr) | | | | | | |

- Fetal Parameters - Live fetal body weights were similar among treated and control groups. Fetal external and visceral examination revealed that one fetus in the 10 mg/kg group with major malformation (elongated nose, right anophthalmia, displaced left eye, displaced ears, no mouth opening, a papillated left flap of tissue located next to the left eye, and missing the left kidney and ureter). Skeletal examination of this particular fetus also showed some alterations (malformations) with the characteristics of split, misshaped, and unossified skull bones. **Based on the data from skeletal examination, the incidence in the wavy ribs appeared to increase in the fetuses at 30 and 100 mg/kg groups with values of 7 in 4 litters and 23 in 7 litters respectively as compared with 5 in 2 litters in the control group.** It should be noted that data from the historical controls should be employed to compare the incidence for alterations (malformations) and variations in the external, visceral, and skeletal examinations.

Therefore, the no-observable-adverse-effect-level (NOAEL) for the maternal, reproductive, and fetal development in the present study was 100, 30, 10 mg/kg/day, respectively.

2.4.2.2. An Oral Study Of Embryo-Fetal Development In The Rat Administered SC-58635 (SA 4599), Document No.: P20S4599; Date: 03-Dec-1997 (Vol. 1.59, p. 1-375)

Included as an appendix to this report was:
Pharmacokinetics Of SC-58635 in An Oral Study Of Embryo-Fetal Development in The Rat Administered SC-58635 (SA4599), Document No.: M3097210; Date: 04-Sep-1997 (Vol. 1.59, p. 353-369)

Study Nº: SA 4599/COV6127-353
Report Nº: P20S4599
Study Aim: To evaluate the maternal and embryo-fetal toxicity and teratogenic potential of SC-58635 when administered once daily via oral gavage to pregnant rats during the period of organogenesis.
Compound: SC-58553 (Lot Nº 95K010-A1A) suspension in 0.5% methylcellulose (w/v) (400 cps) & 0.1% polysorbate 80 (v/v) in $H_2O$
Dose & Route: 0, 10, 30 and 100 mg/kg/day, 10 ml/kg for 12 days (Gestation Days 6-17) by gavage
Control vehicle: 0.5% methylcellulose (w/v) & 0.1% polysorbate 80 (v/v) in $H_2O$, 10 ml/kg
Animals: ♀ Crl:CD®BR rats , ~ 10-11 weeks of age, weighing g at time of mating, 30/group for Toxicology study and 2-6/group for PK study.
Study Location:
Study Date: 6/3/97 - 6/20/97
Compliance with GLP/QAU: Yes
Study Design: Groups of 32-36 pregnant rats were dosed with SC-58635 or vehicle once daily for 12 days (Gestation Days 6-17) by oral gavage. Group assignments and dose levels are as follows:

| Group | Dose | Nº Rats/Group | |
|---|---|---|---|
| | (mg/kg/day) | Toxicology Study | PK Study |
| 1 (Control) | 0 | 30 | 2 |
| 2 (Low) | 10 | 30 | 6 |
| 3 (Mid) | 30 | 30 | 6 |
| 4 (High) | 100 | 30 | 6 |



The following parameters were monitored.

- Mortality and Clinical Signs - 2x/day.
- Body Weight & Food Consumption - Gestation Days 0, 6, 8, 10, 12, 14, 16, 18 and 20.
- PK - on Gestation Days 6 and 17 at 0, 2, 3, 4 and 24 hr post dose.
- Cesarean Section and Necropsy - Gestation Day 20. Each animal were examined for cervical, thoracic, or abdominal visceral abnormalities. Abnormal viscera were preserved in 10% neutral-buffered formalin. The uterus from each gravid female was excised, weighed, and examined for the number and placement of implantation sites, live and dead fetuses, early and late resorptions, and any abnormalities. The uteri of apparently non-pregnant females were stained with ammonium sulfide for verification of pregnancy status. The ovaries were examined for the number of corpora lutea.
- Fetal Examination - Each fetus was sexed, weighed, examined for external abnormalities and sacrificed. Visceral examination was performed on ½ of the fetuses from each litter for assessing soft tissue development. The remaining fetuses were processed for skeletal examination using

the Alizarin Red S staining method. This evaluation included examination of the skull, long bones, vertebral column, rib cage, extremities, and pectoral and pelvic girdles. Bone alignment and degree of ossification were assessed. All fetuses were kept in Bouin's fixative (fetuses examined for visceral abnormalities) or glycerin (fetuses examined for skeletal abnormalities).

**Results:**

- Clinical Observations and Mortality - One ♀ @ 10 mg/kg was found dead on Gestation Day 20 as a result of dosing error (perforated esophagus) with clinical signs of swollen dorsal cervical area, swollen right shoulder, and few or no feces.
- Body Weights and Food Consumption - Significantly lower mean body weight (↓ 4% relative to control) and body weight change (↓ 28.5%) values were noted for the animals @ 30 mg/kg during the pretreatment interval (Gestation Days 0-6). A significant reduction (↓13.6 %) in food consumption was observed for the high dose group during Gestation Days 6-8.
- Gross Pathology - The Group 2 ♀ that died on Gestation Day 20 had a perforated esophagus, a large amount of food in the thoracic cavity and enlarged adrenals. Another Group 2 ♀ had a diaphragmatic hernia. There were no treatment related changes in gravid uterine weights, corrected terminal weights, and net body weight gains. The pregnancy rates were 97, 100, 100, and 100% for the main study females in Groups 1-4, respectively. The mean numbers of corpora lutea and implantation sites and percent preimplantation loss values of the SC-58635-treated animals were comparable to those of the control group. Values for the mean percent of early, late, and total resorptions and viable fetuses were comparable among all groups. There were no dead fetuses and the sex ratios and mean covariate fetal weights were similar among all groups.
- Fetal Evaluations - **A dose dependent increase in diaphragmatic hernia (soft tissue malformation) was noted.** The fetal and litter incidences for diaphragmatic hernia in each group are presented in the following table.

| | | Dose (mg/kg) | | | |
|---|---|---|---|---|---|
| | | 0 | 10 | 30 | 100 |
| **VISCERAL EVALUATION** | | | | | |
| Litters Evaluated | | 29 | 29 | 30 | 30 |
| Fetuses Evaluated | | 209 | 215 | 216 | 221 |
| **Soft tissue Malformations** | | | | | |
| Diaphragmatic Hernia | Fetal Incidence | 0 | 0 | 8 (3.7%) | 31 (14%) |
| | Litter Incidence | 0 | 0 | 6 (20%) | 13 (43%) |
| **SKELETAL EVALUATION** | | | | | |
| Litters Evaluated | | 29 | 29 | 30 | 30 |
| Fetuses Evaluated | | 207 | 218 | 211 | 222 |
| **Skeletal Variations** | | | | | |
| Unossified Vertebral Centrum | Fetal Incidence | 5 (2.4%) | 0 | 3 (1.4%) | 11 (5.0%) |
| | Litter Incidence | 4 (14%) | 0 | 3 (10%) | 7 (23%) |
| Bipartite Vertebral Centrum | Fetal Incidence | 5 (2.4%) | 4 (1.8%) | 1 (0.5%) | 8 (3.6%) |
| | Litter Incidence | 4 (14%) | 3 (10%) | 1 (3.3%) | 7 (23%) |
| 5th Sternebrae Incomplete Ossification | Fetal Incidence | 64 (31%) | 71 (33%) | 88 (42%) | 109 (49%) |
| | Litter Incidence | 23 (79%) | 22 (76%) | 25 (83%) | 29 (97%) |
| Sternebrae Asymmetrically Ossified | Fetal Incidence | 3 (1.4%) | 1 (0.5%) | 12 (5.7%) | 9 (4.1%) |
| | Litter Incidence | 2 (6.9%) | 1 (3.4%) | 9 (30%) | 8 (27%) |
| **Skeletal Malformations** | | | | | |
| Absent Bone in Skull | Fetal Incidence | 0 | 0 | 0 | 1 (0.5%) |
| | Litter Incidence | 0 | 0 | 0 | 1 (3.3%) |
| Vertebral Anomaly with/without Rib Anomaly | Fetal Incidence | 0 | 0 | 0 | 1 (0.5%) |
| | Litter Incidence | 0 | 0 | 0 | 1 (3.3%) |